First International Congress on Diseases of the Chest
Forlanini Institute, Rome, Italy, Sept. 17 - 22, 1950

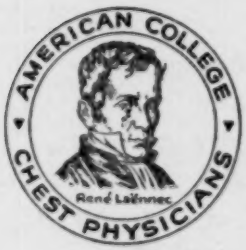
VOLUME XVIII NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



PUBLISHED MONTHLY

JULY
1950

EXECUTIVE OFFICE, 500 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS
PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS

Entered as Second Class Matter August 10, 1936, at the Postoffice at El Paso, Texas
Under the Act of Congress of August 12, 1912.

DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
500 North Dearborn Street, Chicago 10, Illinois
MURRAY KORNFELD, *Managing Editor*

VOL. XVIII JULY 1950 No. 1

CONTENTS:

Entered as second class matter, August 18, 1936, at the postoffice at El Paso, Tex., under the Act of Aug. 24, 1912.

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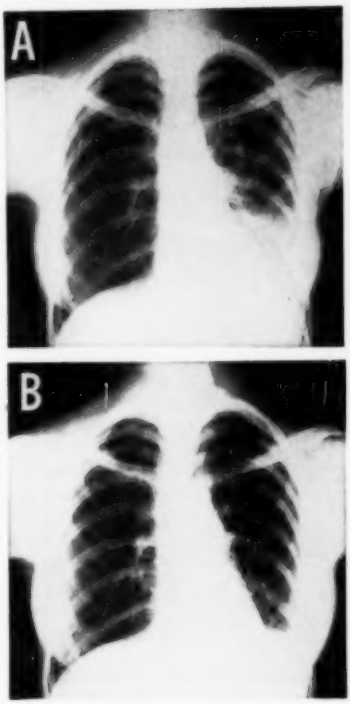

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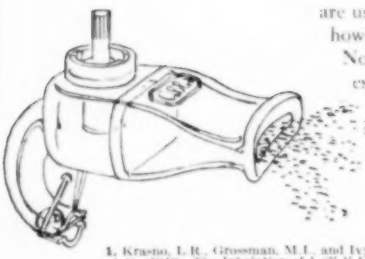

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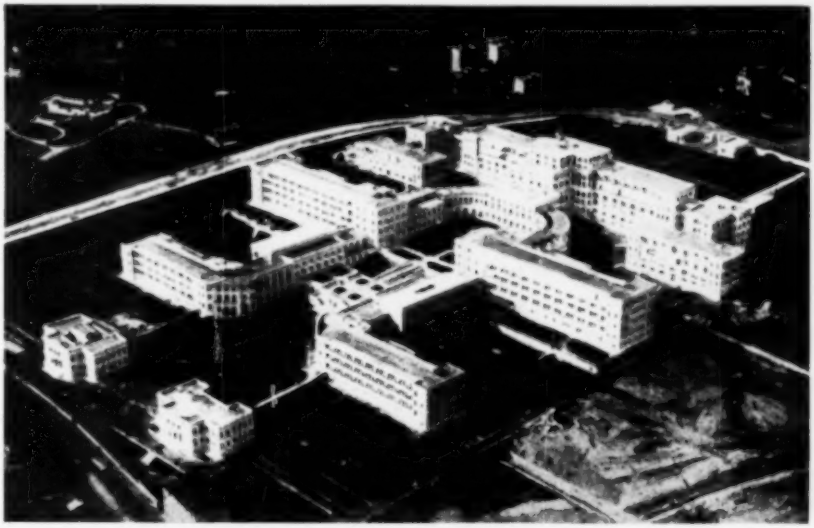

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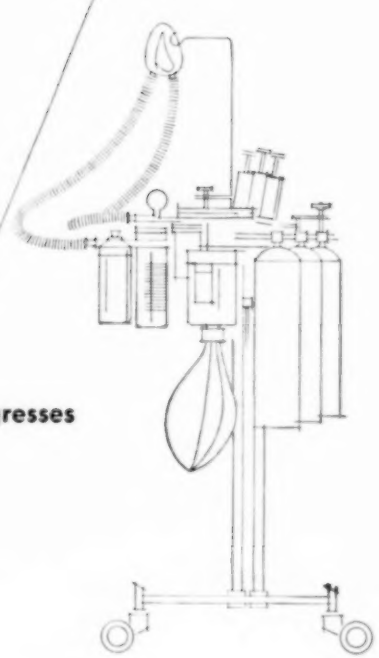

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DISEASES *of the* CHEST

VOL. XVIII JULY 1950 NUMBER 1

Primary Carcinoma of the Lung*

EVARTS A. GRAHAM, M.D., F.C.C.P.†
St. Louis, Missouri

Bronchiogenic carcinoma today is one of the most important cancer problems. From being a rare condition 50 years ago it has become so common in recent years that now there is evidence indicating that, at least in males, it is the most common visceral cancer. It has displaced cancer of the stomach to second place in several large hospitals where statistical studies have been made. For example, Ochsner and DeBakey[1] at the Charity Hospital of New Orleans, Wheeler[2] at the St. Louis City Hospital, and recently Avery[3] at the Hines Veterans' Hospital at Hines, Illinois, have all found that primary carcinoma of the lung is more frequent in those institutions than carcinoma of the stomach.

There has been some discussion as to whether such findings indicate an actual increase or whether rather they are the result of better diagnosis and of the general greater longevity of people nowadays. In my own opinion, however, there can be little doubt that there has been an actual increase in primary carcinoma of the lung. After all, there were excellent pathologists 50 years ago who could hardly have failed to find the primary lesion in the lung in most instances.

If one admits that an actual increase has occurred, then one's curiosity becomes aroused about a possible explanation. The increase seems to be not limited to only this country but to involve the civilized world. Could there be some exogenous carcinogenic factor associated with our culture which might be responsible for this amazing change in incidence of this disease during the last half century?

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*Presented at the 6th Inter-American Congress of Surgery, Chicago, October 21-23, 1949.

†Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri.

When we pursue this line of thought we are at once confronted with the realization that, although in many respects our mode of living has been changed, there are two factors which have been added which may have a direct bearing on our problem. One of these is that the period of the last 50 years represents the era of the automobile and the extensive use of petroleum and its products. It is tempting to assign importance to this consideration, but preliminary studies which have been made seem to show that although there may be a somewhat higher percentage of lung cancer in garage men and workers in the oil industry the incidence is not strikingly different from that in the general population. The second factor is cigarette smoking. Figures from the Internal Revenue Department of the United States Government show an enormous increase in the production and sale of cigarettes during the last 50 years (Ochsner and DeBakey[4]).

Several investigators have attempted to discover what relationship, if any, exists between the great increase in cigarette smoking and the remarkable increase in bronchiogenic carcinoma. Most of this work, however, has been based on the assumption that the use of tobacco is synonymous with cigarette smoking, an assumption which at least is open to question. Tylecote,[5] in 1927, was one of many who suggested that smoking is an important etiologic factor. Hoffman[6] in 1931, thought there was strong statistical evidence that tobacco is an important factor in the increase of lung cancer. Roffo[7] in 1937, was able to produce experimental cancer in rabbits' ears by the application of tobacco tars. In 1941 Ochsner and DeBakey[4] called attention to the similarity of the curve of increased sales of cigarettes in this country to the greater prevalence of primary cancer of the lung in the human, and they emphasized the possible etiological relationship of cigarette smoking to the condition. Later, however, they seemed to be more doubtful of this relationship.[8] At the present time Wynder and I, with the cooperation of many other surgical clinics, are making a statistical study of this relationship.

It is too early to give even a preliminary report of this study, but it can be stated that in 500 cases of proved bronchiogenic carcinoma it has been rare to encounter a man with a squamous (epidermoid) bronchiogenic carcinoma who had not been an excessive cigarette smoker for years, or at least who had not formerly smoked cigarettes excessively. By "excessive" smoking is meant more than one pack a day. It should be emphasized that it is not necessary that at the time he should be an excessive smoker, because from the abundant work on the experimental development of cancer in animals it is well known that there is a considerable time lag between the application of the carcinogenic

agent and the development of the cancer, which in the human apparently may be a matter of five years or more. The use of tobacco in other forms, as in pipes and cigars, appears not to bear the same important relationship. It would seem, therefore, that if smoking is an etiological factor, it is either the greater inhalation of cigarette smoke or something in the composition of cigarettes which contains the carcinogenic agent. Various possibilities suggest themselves, perhaps something used in the curing of the tobacco, insecticides employed during its growth, or maybe even something in the paper.

The remarkable etiological relationship between cigarettes and bronchiogenic carcinoma which seems to be developing applies chiefly ,if not entirely, to squamous, or epidermoid, carcinoma. This is the carcinoma which is by far the most common lung tumor, and it is the one which has shown the striking increase. It is overwhelmingly a male disorder (in our last 75 cases 18 males to one female). It arises usually in a major bronchus and it represents a transformation of adult epithelium into cancer tissue. In our experience when a woman has such a tumor almost invariably she is or has been a heavy cigarette smoker. It is a common belief that, at least in this country, women are as much or even more addicted to cigarette smoking than men. However, a statistical study of this question, not yet published, indicates that only about 40 per cent of the women of cancer age smoke at all and of these only a small percentage smoke to excess. The younger women who have not yet reached the cancer age are more likely to be heavy smokers.

By contrast the adenocarcinoma is a tumor which occurs about equally often in the two sexes, but slightly more in the female. It is much less common than the squamous or epidermoid type, and it seems to be influenced slightly, if at all, by cigarette smoking. There is considerable evidence that in at least many cases this tumor begins as a so-called bronchial adenoma. It seems to represent a transformation of embryonic epithelium into cancer tissue, rather than a change of adult epithelium into cancer cells as in the case of the epidermoid type. It is therefore to be regarded as an entirely different condition from the ordinary squamous cell bronchiogenic carcinoma.

Many histological varieties of bronchiogenic carcinoma have been created by the pathologists. Thus some are designated as undifferentiated, as oat cell or round cell, others as alveolar carcinomas. There is some evidence, however, which justifies a conception that these types are only variants of the two main kinds of bronchiogenic carcinoma, namely the squamous or epidermoid and the adenocarcinoma. It will be impossible to discuss

here the evidence for this conception, but the interested reader may find a further discussion of the idea in other publications of ours.[9-11]

The two principal types of primary carcinoma of the lung which I have been discussing are bronchiogenic in the sense that they arise within or close to a bronchus which is usually a major one. Recently there has been discovered another type which apparently begins in the parenchyma of the lung and perhaps actually in the alveolar epithelium. When first found this tumor is generally confined to one lobe, although multiple nodules or foci of cancer are present throughout the lobe. From the gross appearance it may be difficult to be certain whether the lesion is malignant or inflammatory in nature. In most instances, even if the diseased lobe is removed, the condition becomes evident in the remaining lobes of the same lung after months or years and even in the other lung. In the microscopic appearance and in some of the clinical features (especially the presence and the discharge of a large amount of mucus) there is a striking resemblance to the disease of sheep known as "jagziekte."[12] This disease is known to occur sometimes in epidemic forms in sheep, and it is supposed to be due to a virus which as yet has not been found. This disease has also been described sometimes under the name of "multiple adenomatosis."[13] Case reports of this most recently discovered type of primary cancer of the lung will be found referred to in a recent article of ours.[14] In addition, Stephens and Shipman[15] of San Francisco reported a case at the last meeting of the American Association for Thoracic Surgery. More extensive recent articles are those of Swan[16] and of Laipply and Fisher.[17]

Clinical Features

Because of the frequency of primary carcinoma of the lung it is highly important that every doctor should be familiar with its principal features. There is nothing pathognomonic in the clinical history. However, in a typical case there is cough with blood streaked sputum and a shadow in the x-ray which is generally seen as an uncircumscribed abnormal density in the region of the hilus. These features are so commonly found in most cases that it is imperative to proceed with the necessary additional examinations. In fact, the burden of proof is on anyone who doubts the presence of a bronchiogenic carcinoma under such circumstances. Of course, there are many variations from this more or less typical clinical picture. For example, if the tumor arises in a small bronchus there may be but little cough and sputum with perhaps no expectoration of blood. In such a case the x-ray shadow is often spherical and rather sharply circumscribed at a

distance from the hilus. In other cases the tumor arises in the apex of a lung and the first suspicion of its presence may come from the pain experienced by the patient because of the invasion of the brachial plexus or intercostal nerves. In still other cases the complicating infection of the tumor with its attendant fever may be the first symptom of illness noted by the patient; or again, more rarely, the presenting symptom may be from a metastasis in the brain or in a bone.

Whenever suspicious evidence is present it becomes an urgent and compelling matter to pursue the necessary special examinations. Of these there are two which stand out as particularly important; bronchoscopy and examination of the sputum for cancer cells, preferably by the Papanicolaou method.[18]

Unfortunately, many tumors arise in bronchi too small or too unfavorably situated to be seen with the bronchoscope. In our own experience only about 60 per cent of them can be visualized adequately enough to obtain tissue for a biopsy. The additional examination of the bronchial washings and sputum will give a higher percentage of positive diagnosis, although actually, as in the use of the bronchoscope, in our experience we obtain only about 65 per cent of positive results. The advantage, however, of supplementing a negative bronchoscopic examination with sputum examination is that in some cases a positive diagnosis can be made in that way. Similarly sometimes a positive bronchoscopic diagnosis can be made although the sputum examinations have been negative. It must be realized, however, that the search for cancer cells in the sputum must be made by an expert. There is a very great danger of reports of both false positives and false negatives when the examinations are made by one who is not thoroughly familiar with the cytology of the secretions which he is examining. The use of the bronchoscope should not be neglected even if a positive diagnosis has been made by sputum examination. Very valuable information can often be obtained by the use of this instrument which a study of the sputum alone will not yield. For example, there are the questions of the proximity of the growth to the trachea, the fixation of the carina, etc.

After using all the standard methods of examination there will remain about 30 or 35 per cent of cases in which, in spite of a suspicious clinical history and suggestive x-ray films, it has been impossible to establish a positive diagnosis. What shall be the disposition of those cases? Unquestionably, in my opinion, the best thing to do under such circumstances is to perform an exploratory operation. In most instances at operation the diagnosis can be readily established by direct inspection and palpation. If there is still doubt it is nearly always possible to remove some tissue

for an immediate frozen section. Experience shows that when the clinical history and x-ray examination are suspicious the exploratory operation will nearly always reveal the presence of a carcinoma even when no positive evidence has been obtained by bronchoscopy and cytological examination of the sputum.

Until 1933 the question of establishing the diagnosis of bronchiogenic carcinoma was largely a matter of only academic interest because there was no successful treatment. In April of that year, however, the writer[19] was fortunate in having presented to him a patient with a squamous carcinoma of the left upper lobe bronchus which was not too far advanced for radical treatment. At operation the left lung was completely removed in one stage, and the patient made a completely satisfactory recovery. He has had no recurrence. He is a physician who is carrying on an active practice more than 16 years after his operation. This happened to be not only the first successful total pneumonectomy for cancer but also the first successful one-stage pneumonectomy performed for any reason.

The operation of one-stage total pneumonectomy has now become by common consent the preferred treatment for primary carcinoma of the lung. By this operation it is easier to remove possibly invaded lymph glands; and, by analogy with well established surgical principles in treating cancer of other organs, the disease is more likely to be eradicated by the removal of the whole organ than by the removal of only a part, as by a lobectomy. The high operative mortality in the early days of nearly 50 per cent has been reduced to one now of 10 per cent or less. In 139 consecutive operations of total pneumonectomy for carcinoma in a period comprising the last four years and seven months from January 1, 1945, to August 1, 1949, at the Barnes Hospital we have had 12 hospital deaths, an operative mortality therefore of 8.4 per cent. Since the first successful one-stage total pneumonectomy on April 5, 1933, we have performed the operation on 367 patients. Of more importance than the operative mortality in cancer of the lung is the question of five year freedom from recurrence. In our own experience our results indicate that 28 per cent of our patients are free from recurrence after five years. Of those with glands involved there have been 15 per cent of five year survivors. In another five years there will probably be a higher percentage of survivors, because the operative mortality is considerably lower now than it was 10 years ago.

Ochsner, DeBakey and Dixon,[20] in 1947, stated that in an experience of 11 years from January 1, 1936, to December 1, 1946, they had performed 129 pneumonectomies for cancer with a hospital mortality of 24.8 per cent and with a survival rate of 22 per

cent for five years or more. Rienhoff,[21] also in 1947, stated that he had performed 112 pneumonectomies for cancer with a hospital mortality of 22 per cent and a survival rate of 10.7 per cent for a period of five years or more. Too much importance should not be placed on mortality rates, because some surgeons are probably more conservative than others in the selection of their cases for operation. Probably we have been more conservative than the authors just mentioned. The important fact is that the results of many surgeons show that the condition is curable if the operation is done early.

One of the most distressing features of the whole problem is the large percentage of patients who present themselves with the cancer too far advanced for a successful operation. Although we have made an exploratory operation in about 40 per cent of the cases, we have been able to perform a pneumonectomy in only 25 per cent of the patients who present themselves with proved primary carcinoma of the lung. In almost all cases the reason has been that the cancer was too far advanced. In a few cases the operation has not been performed because the patients were considered to be too bad risks for reasons of being too old, bad heart disease, etc. My oldest successful pneumonectomy was in a patient 75 years of age. Very old people do not tolerate the operation well.

The features which in general lead us to decline to operate are (1) cachexia from advanced cancer; (2) evidence of nerve involvement ,such as severe pain, paralysis of a vocal cord (usually the left), and paralysis of the corresponding half of the diaphragm; (3) the presence of demonstrable metastases in other organs, notably the brain, liver, bones, etc.; (4) the presence of pleural fluid which is found to contain cancer cells; (5) extension of the growth into the wall of the trachea. At exploratory operation very often the cancer is found to have invaded the large vessels or to involve the mediastinal glands to such an extent that obviously all the tumor cannot be removed. Again, sometimes the cancer is disseminated over the parietal pleura in small nodules. If, however, only a localized invasion of the chest wall is found, we prefer to remove that portion of the wall with the lung.

The question of palliative pneumonectomy frequently arises. There is no doubt that a patient will become greatly improved after the removal of a cancerous lung which contains an abscess or a considerable amount of infection. In other cases, however, in which infection is not a prominent feature there is some doubt as to how much palliation will be accomplished when tumor tissue in large amount is left behind. Also, there always remains the possibility of making the patient more uncomfortable if the bron-

chial stump breaks open because of some cancer tissue which prevents its healing. Of course, there will be a difference of opinion on this whole question. We find at the Barnes Hospital that in the majority of cases which we explore but do not remove the lung the conditions present, such as involvement of the great vessels, make the technical procedure of pneumonectomy impossible.

SUMMARY

1) Primary carcinoma of the lung has shown a remarkable increase in the last half century, to become perhaps the most frequent visceral carcinoma in the male sex.

2) Apparently some exogenous carcinogenic factor, inherent in our recent culture, must be responsible for this dramatic increase.

3) The possibility of cigarette smoking as one of the factors is briefly discussed.

4) Bronchiogenic carcinoma is no longer, as formerly, a hopeless condition. It is curable by total pneumonectomy if the surgeon gets the patient early enough.

RESUMEN

1) El carcinoma primitivo del pulmón ha demostrado un notable aumento en los últimos cincuenta años, para venir a ser probablemente el carcinoma visceral más frecuente en el sexo masculino.

2) Aparentemente algún factor carcinogénico, exógeno, inherente a nuestra cultura debe ser responsable de este dramático aumento.

3) La posibilidad de la influencia del fumar cigarrillos se discute brevemente.

4) El carcinoma bronquiogénico ya no es como antes una condición desesperada. Es curable por la neumonectomía total si el cirujano toma a su cargo al enfermo tempranamente.

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Tolerance and Effects of Lupulon in Man*

S. M. FARBER, M.D., F.C.C.P., J. M. MASTEN, M.D.,
H. H. ANDERSON, M.D., R. W. GENTRY, M.D.
and Y. C. CHIN, Ph.D.†
San Francisco, California

Introduction

It is recognized that the antibacterial therapy of tuberculosis has lagged behind that of other infectious diseases. While streptomycin has given clinical evidence of efficacy, this antibiotic alone is not entirely as satisfactory as it is in conjunction with collapse therapy. Antibacterial therapy of mycobacteria differs from that of other infectious diseases primarily because of the chronicity of infection.[1] In addition, the proliferative and destructive changes of host's tissues are definite disadvantages, from the standpoint of its chemical control.

Pathologic changes may prevent adequate access of an antibacterial agent to causative micro-organisms, and further, the tissue changes may be so profound that their reversibility is not possible by means of chemical agents in readily tolerated amounts. At best, suppression of the infectious process appears to be the most easily attainable goal, thus permitting natural defenses of the body to completely overcome the infectious process. It is further recognized that many forms of tuberculosis tend toward recovery with the general medical and surgical procedures now employed.

As stated by Pfuetze and Pyle,[1] the chief impediment to more effective therapy with streptomycin, has been the high incidence of bacterial resistance after the antibiotic has been used for a few weeks or months. Streptomycin is believed to be useful in three ways: as definitive therapy, as palliative treatment, and as an adjunct to surgical procedures. Since it is recognized that streptomycin alone cannot be relied upon for definitive treatment in pulmonary tuberculosis, combined therapy is now being utilized with such agents as promin, diasone, and p-aminosalicylic acid. In the continued search for a satisfactory preparation in the

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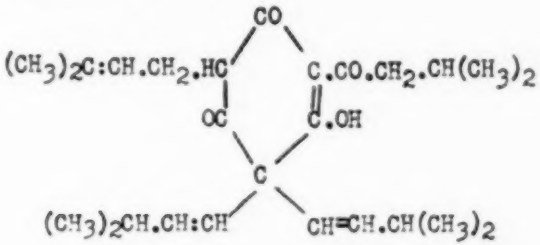
Presented before the Pacific Coast Section, American Association for Advancement of Science, Vancouver, B. C., June 17 and 18, 1949.

treatment of this disease, the antibiotic properties of a new agent, lupulon, have undergone scrutiny.

Development

Lupulon is one of two antibiotics derived from the soft resins of hops (*Humulus lupulus*).[2,3] According to Wieland[4] and Wollmer[5] it has the chemical structure:



It is a colorless, odorless, and tasteless crystalline substance that is lipoid soluble, unsaturated and sensitive to oxidation. It has a melting point of 88 to 92 degrees C. and a solubility in water at pH 5.9 of 12 mgm./1.

The toxicity of lupulon was determined in inbred white mice.[6] Daily intramuscular administration of one-tenth of the acute LD_{50} as 1.5 per cent lupulon crystals in cottonseed oil over a period of four weeks was tolerated without gross evidence of harmful effect. Histopathologic examination of tissue from these animals revealed small areas of leukocytic infiltration in the liver as well as foci of degeneration in the renal tubules.

In vitro tests with lupulon against tubercle bacilli (H37Rv) in Dubos fluid medium showed consistent inhibition of mycobacterial growth at a dilution of 1:40,000. This was altered neither by the substitution of other wetting agents for the "Tween 80" in Dubos medium nor the presence of sub-bacteriostatic concentrations of other antituberculous substances such as promin, streptomycin, subtilin, and dimercaptopropanol (BAL).

The antituberculous activity of lupulon was tested *in vivo* using groups of mice infected intravenously with 0.02 mgm. of the H37Rv strain of *M. tuberculosis* grown in Dubos medium. One-tenth the LD_{50} was administered by two different routes, intramuscularly as a single daily dose and intragastrically at 12 hour intervals. As determined by histopathologic sections stained with hematoxylin and eosin for lesions and by acid-fast methods for determining the abundance of tubercle bacilli, lupulon exerted considerable suppressive effect on the development of tuberculosis. Treated animals had fewer lesions in all but cardiac tissue; but more

remarkable was the significant reduction in number of microorganisms in the liver (34 to 1), heart (8 to 1), spleen (4 to 1), lungs (3 to 1), though not in the kidneys.

Antituberculous activity both *in vitro* and *in vivo*, together with a relatively low toxicity, suggested possible application of this antibiotic to man. The greater solubility in lipoids, with its greater partition coefficient, may serve to make lupulon more available to the waxy coat of mycobacteria. In this respect it may differ from other available antituberculous agents, and thus provide an explanation for its potency against tubercle bacilli. For these reasons, it was deemed desirable to consider the oral application of lupulon to tuberculous patients.

The first 10 patients given lupulon orally ranged in age from 25 to 43 years and included members of both sexes. Nine had moderately advanced pulmonary tuberculosis. There was one with tuberculous laryngitis and one with minimal tracheo-bronchial disease in addition to the pulmonary disease.

Administration and Absorption

Lupulon* was supplied in gelatin capsules each containing approximately 0.5 gram. Each patient was given a daily dose of 5.0 grams regardless of weight. The antibiotic was administered orally in one gram amounts every four hours between 6:00 a. m. and 10:00 p. m.

Of the 10 patients beginning therapy, five completed three months, one two months, two 50 days and two a week or less. The latter four developed complications or side reactions requiring discontinuance of the medication.

The Western Regional Research Laboratory, Albany, California, has developed a spectrophotometric method for the assay of blood levels during therapy.[7] The details of the procedure have not yet been published. It is evident, however, that detectable amounts of the antibiotic occurred in each of the seven patients tested at regular intervals over eight weeks. These ranged from 1.9 to 6.5 gamma per ml., which were beyond the range of control sera obtained from untreated patients.

Clinical and Laboratory Studies

In an effort to determine the action and possible toxicity of lupulon, in addition to complete physical examination and chest roentgenograms, the following procedures were performed on each

*We are indebted to Drs. Jas. C. Lewis and W. D. Maclay of the Western Regional Research Laboratory, U. S. Dept. of Agriculture, Albany, California, for their constant help and for generous supplies of lupulon used in this study. Mr. S. J. Dean, Jr., Manufacturing Laboratory, College of Pharmacy, University of California made up capsules in appropriate sizes.

patient: complete blood count, urinalysis, measurement of the daily sputum volume, determination of the erythrocyte sedimentation rate and the concentration of non-protein nitrogen and creatinine in the blood and protein in the serum, albumin-globulin ratio, icterus index, cephalin flocculation and thymol turbidity. Liver function was also determined by the hippuric acid test and renal function by the phenolsulfonphthalein and Mosenthal tests. Electrocardiograms were obtained routinely and bronchoscopies were routinely done in most of the cases.

Tubercle bacilli were present by direct smear in the sputum of all patients prior to onset of therapy. These were verified by positive cultures in all but two of the cases.

During therapy the following procedures were carried out at regular intervals; daily measurement of sputum volume, urinalyses every second day, and weekly complete blood counts, chemical analyses of the blood and cultures and smears of three-day sputum concentrates. The erythrocyte sedimentation rate, phenolsulfonphthalein test and electrocardiograms were repeated at approximately monthly intervals.

The progress of the disease was followed during and after therapy by means of frequent physical and laboratory examinations and chest roentgenograms.

Clinical Observations: While under therapy with lupulon, three patients had significant decreases in the daily volume of sputum and in the frequency and intensity of their cough. Three had significant weight losses, ranging from 9 to $5\frac{1}{2}$ pounds while that of the others remained essentially unchanged.

All but one of the patients were essentially afebrile when lupulon therapy was instituted. No alteration in body temperature occurred in these individuals. One patient had a daily temperature elevation to 101 degrees F. prior to the institution of lupulon therapy which continued throughout the period of therapy. Another demonstrated an increase in extent and severity of an ulcerative tuberculous laryngitis while receiving lupulon.

One patient had significant roentgen evidence of improvement of the pulmonary lesion. None of the others showed changes which could be attributed definitely to the medication.

Repeated laboratory studies failed to reveal any alteration in hepatic or renal function during or after therapy. Serial electrocardiograms demonstrated no change during or after therapy.

Bacteriologic studies have shown to date that the concentrated sputa of three patients became negative for tubercle bacilli on smear and culture after therapy. The others have shown little change in bacteria present in the sputum.

Toxicity: No toxicity of liver, kidney, bone marrow, or myocar-

dium was evidenced either clinically or by laboratory tests.

Every patient experienced some degree of gastro-intestinal irritation while receiving lupulon. Characteristically there was noted epigastric sensation of burning and lower abdominal cramping which occurred from five minutes to six hours after taking the first dose of the drug. These symptoms were sometimes associated with watery diarrhea which was not completely controlled by bismuth subcarbonate or other agents. Nausea and vomiting, when present, continued for the first two days to one and a half weeks of therapy. Lupulon was discontinued in two cases during the first seven days because of gastrointestinal disturbance. Patients continued to be mildly anorexic after the cessation of these symptoms.

Two patients developed transient mild frontal headaches. Two complained of light-headedness. No neurologic changes have been observed. The causal relationship between lupulon and the above complaints is difficult to assess. Two patients noted slight somnolence during the first week of therapy.

Hypersensitivity reactions were uncommon, and the relationship of these reactions to the drug is not clear. One patient developed an erythematous macular rash lasting two days and a generalized myalgia of five days' duration. Two individuals demonstrated a transient eosinophilia.

COMMENT

The evaluation of the antituberculous effect of any antibiotic requires a period of months to years. Thus, conclusions from this investigation are not warranted. However, there is a suggestion of therapeutic activity at a daily oral dose of 5.0 grams. In one patient there was definite laboratory and clinical improvement, three were freed of the mycobacterium during therapy, and a similar number had significant reduction in sputum and cough. This evidence together with minimal toxicity, with the exception of gastro-intestinal irritation, affords stimulus for continued study.

An appraisal of the possible development of drug resistance with lupulon is now being made. The effective dose range and most suitable method of administration are yet to be established.

Lupulon in its present form has no place in the treatment of tuberculosis other than purely for investigative purposes.

COMENTARIO

La estimación del valor antituberculoso de cualquier antibiótico requiere un periodo de meses o años. Así las conclusiones de esta investigación no son sólidas. Sin embargo, hay una sugestión de efecto terapéutico con una dosis diaria de 5 gms. orales. En un enfermo hubo mejoría definida según el laboratorio y la clínica.

Tres se libraron de sus bacilos durante el tratamiento y un número similar ha tenido reducción de la tos y de los esputos. Esta evidencia además de la toxicidad mínima, con excepción de la irritación gástrica, alienta para continuar el estudio.

Se trata ahora de averiguar si se desarrolla resistencia al lupulón.

Aún no se ha establecido el alcance efectivo de la droga ni el más adecuado método de administración. El lupulón en su forma presente no tiene lugar aún en la terapéutica de la tuberculosis, sino con fines de investigación.

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The Diagnosis of Bronchial Stenosis*

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Bronchial stenosis is an important pathologic condition which should be recognized clinically. Many times obstruction to a bronchus is the only lesion and is entirely responsible for the symptoms of the patient. Again, it may follow other diseases in the thorax, but it prevents recovery or greatly aggravates the primary condition.

Bronchial stenosis can be recognized by correct interpretation of the findings on physical examination, fluoroscopy, x-ray film, and bronchoscopy. The physical signs of bronchial obstruction are important because they may lead to early diagnosis as in bronchogenic carcinoma; or may modify therapeutic procedures as in pulmonary tuberculosis.

A bronchus may be obstructed in one of three ways: (1) intrabronchially, as a result of impaction with endogenous or exogenous bodies; (2) endobronchially, as a result of intrinsic disease of the channel; and (3) extrabronchially, as a result of pressure or actual invasion of the lumen by pathologic processes in neighboring organs. Thus, it may be seen that almost every conceivable disease of the chest—pulmonary, mediastinal, cardiac, vascular, esophageal and vertebral—may cause an obstruction to a bronchus. Table I will illustrate some of the many factors that may produce one of the three main groups of bronchial obstruction.

It is the purpose of this article to point out the method of diagnosis of the usual single factor of stenosis, and to deal not with the wide-spread obstructive factors that occur with definite clinical pictures such as laryngeobronchitis, asthmatic bronchitis, chronic bronchitis, and bronchiolitis, but with such conditions as bronchogenic neoplasm, foreign body and benign neoplasm. In other words, the conditions that set up a single spot of narrowing of the bronchus. Also this article restricts itself to cases with a partial occlusion, where a narrowing occurs rather than total occlusion of the lumen.

The physiology of the respiratory system requires an open air-

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The opinions herein expressed are those of the writer and do not necessarily represent the views of the Bureau of Medicine and Surgery, Navy Department or of the Naval Service at large.

way. Any obstruction to the bronchi leads to a series of physiologic disturbances. It depends on several factors as to what occurs: (1) the site of the obstruction, whether in a main bronchus or secondary rami, and whether one or several bronchi; (2) the degree and character of the obstruction, whether partial or complete; (3) the time taken for the development of the obstruction; (4) the cause of the obstruction, whether intraluminal, or extrabronchial; (5) the condition of the surrounding lung, with respect to the presence of infection during the period of obstruction; (6) the status of the pulmonary and systemic circulations.

As the degree of the obstruction becomes greater, a check-valve mechanism may result, allowing the inflow of air, but preventing its out-flow, consequently the bronchopulmonary segment distal to this obstruction becomes overinflated. The reason for this is

TABLE I

Bronchial Obstruction

Introbronchial Obstructions:

A. Endogenous
   Tenacious sputum, fibrinous casts, broncholiths, ruptured lymph nodes, postoperative retention of secretion.

B. Exogenous
   Foreign bodies.

Endobronchial Obstructions:

A. Congenital abnormalities.

B. Nonspecific inflammations of the bronchial mucosa or scars.

C. Specific inflammations
   Tuberculosis, syphilis, leprosy, etc.

D. Bronchogenic neoplasms
   Benign, malignant.

E. Distortion of the bronchi.

Extrabronchial Obstructions:

A. Enlarged lymph nodes
   Inflammatory, neoplastic, pneumoconiotic.

B. Mediastinal pressure
   Suppuration, neoplasms, tumors, lymphoblastoma, cysts.

C. Vertebral pressure
   Tumors, abscesses.

D. Tumors of either the lung, esophagus, or intrathoracic goitre or thymoma.

E. Cardiovascular factors
   Dilated left auricle, aortic aneurysm, pulmonary artery aneurysm, congenital abnormalities.

F. Foreign bodies
   Esophagus, intrathoracic.

that the bronchi normally become narrowed during expiration, thus, allowing the air to be trapped by the obstructing lesion. In this manner an obstructive emphysema results. This is clearly seen in the diagram by Jackson first describing this mechanism[1] (Figure 1).

When the obstruction is of such a nature as to produce full occlusion even in inspiration, then inflow as well as out-flow of air is prevented. Thus, the affected bronchopulmonary segment becomes atelectatic. The air is absorbed by the blood in the capillaries. This causes an increased negative pressure intrapleurally. In addition the increased negative pressure may cause fluid to be drawn from the already congested capillaries into the alveoli. Also Drinker[2] and Susman, et al.,[3] have demonstrated that increased resistance to the inflow of air in the bronchi or trachea can produce pulmonary edema by themselves. Short[4] has shown

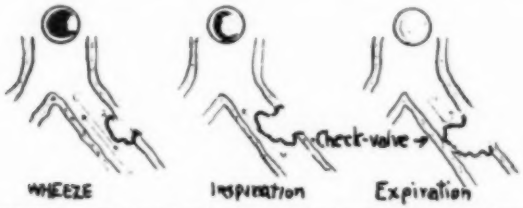

FIGURE 1: The mechanism of valvular production of obstructive emphysema. The growth is seen to obstruct the bronchus when the bronchus is narrowed during expiration and trapping air distal to it. The bronchoscopic view is above the scheme. (Reproduced from Jackson and Jackson's "Diseases of the Nose, Throat and Ear," published by Saunders and Company; with permission of the authors and publishers).

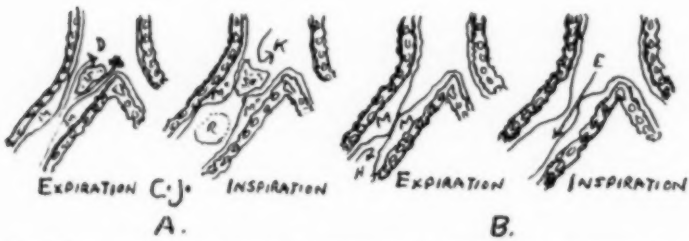

FIGURE 2: A. The mechanism of obstructive atelectasis as produced by inflammed swollen mucous membrane with a small mass of secretion (S) acting like a check-valve. Expiration allows the mass to be lifted up by the air current. Inspiration wedges the secretion and prevents the entrance of air. If the mass is located at (R) then the exit of air is prevented and as in Figure 1 obstructive emphysema results.—B. Merely another condition which can also produce obstructive emphysema by swollen mucous membrane, which closes the lumen during expiration when the bronchus is narrower. (Reproduced from "Diseases of the Nose, Throat and Ear," by Jackson and Jackson, Saunders and Company, with permission).

that accumulation of bronchial and tracheal secretions can lead to slow asphyxia and result in the development of pulmonary edema. All of these factors are present in bronchial obstruction. Thus, a "drowned" lung occurs. This sets up an excellent medium for infection.* The increased negative intrapleural pressure causes a greater inflow to the right auricle which may overload the heart and also in turn produce a tendency to pulmonary edema. Pulmonary edema is not uncommonly seen in patients with an obstructive neoplastic lesion. The mechanism of this type of obstruction is illustrated in the diagrams of Jackson (Figures 1, 2, 3).

From the clinical viewpoint, bronchial obstruction can be deduced by taking a careful history. If a story of wheezing can be elicited from the patient, then the first clue is found. A cough is invariably present; it may be a dry cough. If the obstruction is high, a severe cough may be present; and if the main stem bronchi or trachea is involved, a brassy cough. The larger bronchi often give the wheeze which is noticeable by the patient. If sputum is present, it is usually thin and frothy because of the associated pulmonary edema. The sputum is purulent and foul only when infection has occurred. One can see how these symptoms can be easily confused with cardiac failure.

In tuberculosis, bronchostenosis is suspected when there are episodes of sputum retention with marked, sudden fluctuations in the amount of the sputum.[5] A story of dyspnea on change of position may be the only clue to the presence of a bronchial obstruction. This positional dyspnea may be present when the patient is erect and alleviated by the supine position. This is a most suggestive sign and certainly will negate the assumption of cardiac disease as a cause of the dyspnea.

The physical finding of rhonchi is the characteristic and pathognomonic sign of bronchial stenosis. These were classically described by Laennec[6]: "I apprehend it can hardly exist in bronchial tubes of small diameter." And, "It would seem to depend rather on some alteration in the shape of the tubes through which air passes, and I am disposed to attribute it in most cases to the contraction from some cause or other, of the origin of the bronchial branch. This contraction may be either permanent or temporary, and may be occasioned by pressure of an enlarged gland, or of a circumscribed spot of inflammation, the presence of a tenacious clot of mucous, or the local thickening of the mucous membrane."

*Some of the roentgenologic appearances called atelectasis are really reduced aeration of a portion of lung due to infection, fibrosis, and pulmonary edema. Atelectasis occurs early and is reversible. These conditions are not reversible.

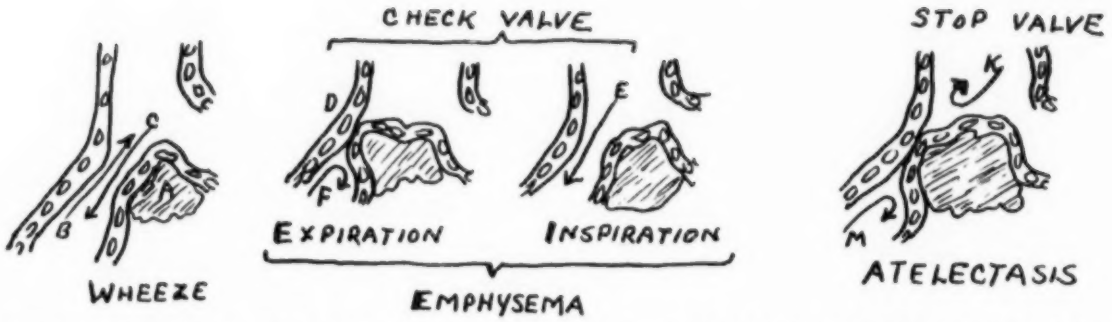

FIGURE 3: Schematic diagram of the mechanism that causes the wheeze, and the check valve mechanism that results in the obstructive emphysema, and also the stop valve mechanism that produces the atelectasis. (Reproduced by permission of Chevalier Jackson and the publishers Saunders and Company, from "Diseases of the Nose, Throat and Ear."

These rhonchi then are the important sign. They are persistent dry sonorous rales unrelieved by cough. In distribution they are local or general, and in character they may be sibilant, but in a great many instances they are predominantly or exclusively sonorous. The sign is more marked during expiration and *may be heard only at the end of a forced expiration*. The great majority of cases exhibited the sign only at the end of a forced expiration. This is attributed to the narrower caliber of the bronchus during this phase of respiration. The rhonchi are usually more readily palpable and invariably loudest over the stenotic bronchus. This was pointed out by McConkey and Gordon[7] and may be seen in Figure 4. It is this localization that differentiates it from such conditions as asthma and chronic bronchitis. These same authors and Kegel[8] pointed out that in certain instances the rhonchi cannot be elicited, except when the patient is lying on the side of the affected bronchus with the shoulder depressed as seen in

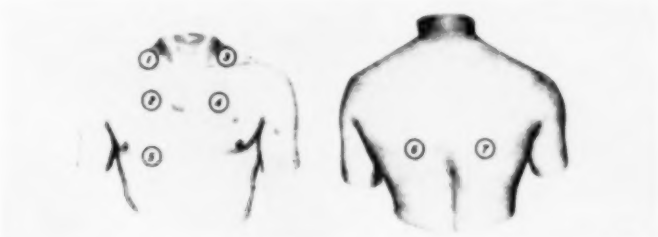

FIGURE 4: The rhonchi are loudest and usually palpable at points 1 or 2 in stenosis of the right main bronchus or its branch to the upper lobe; at points 3 or 4 in stenosis of the left main bronchus or its branch to the upper lobe. In stenosis of the middle lobe bronchus, the area of intensified rhonchi is at point 5; for the left lower lobe, at point 6, and for the right lower lobe bronchus at point 7. (Reproduced with permission of American Review of Tuberculosis, and the authors).

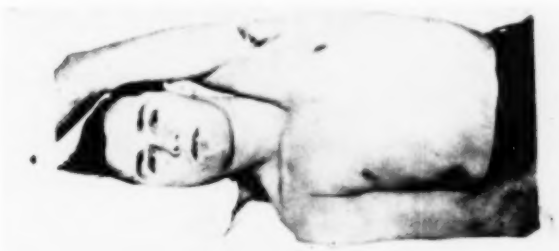

FIGURE 5: Patient lying on side of affected bronchus with shoulder depressed, a procedure helpful for the elicitation of the rhonchi described. (Reproduced by permission of the authors and the American Review of Tuberculosis).

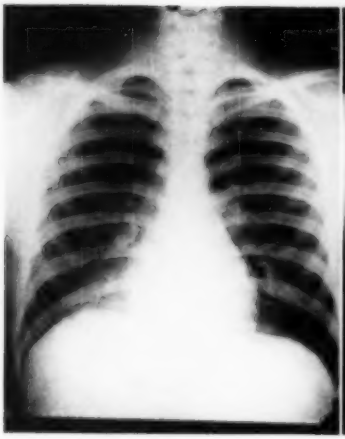

FIGURE 6

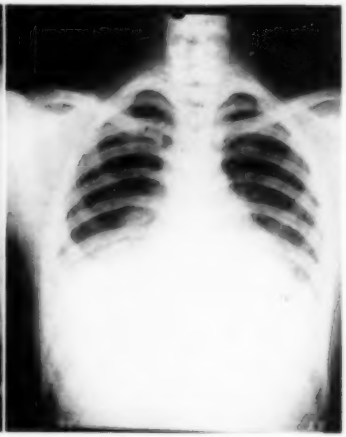

FIGURE 7

Figure 6: Postero-anterior x-ray film of the chest in full inspiration in a case of bronchial adenoma located in right lower lobe bronchus.—*Figure 7:* The same as in Figure 6, in full expiration showing the shift of the mediastinum to the left side. The trapped air in the right lower lobe cannot be visualized as well as it was by fluoroscopy.

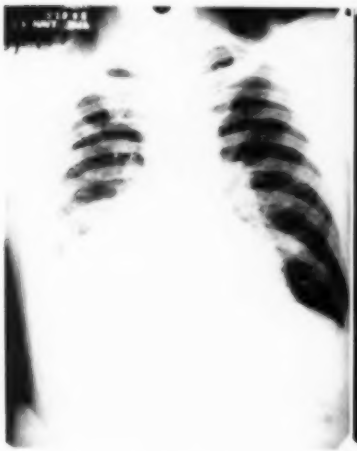

FIGURE 8

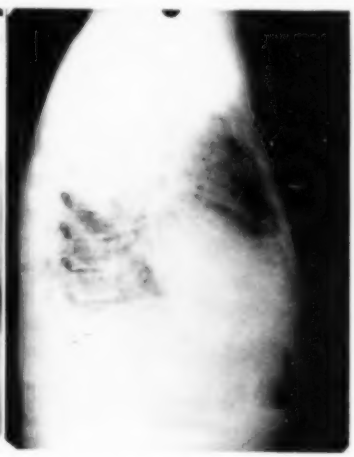

FIGURE 9

Figure 8: Postero-anterior x-ray film of the chest of a case of bronchogenic carcinoma of the right middle lobe producing atelectasis of the corresponding lobe.—*Figure 9:* Right lateral x-ray film of the same case as Figure 8, showing the atelectasis of the right middle lobe. On fluoroscopy on full inspiration, this case showed the mediastinal shift to the right.

Figure 5. This procedure in my hands has been found exceedingly valuable and is invariably present when combined with a forced expiration. The dependent position of the bronchus probably adds to its further narrowing and then gives forth the sign.

This simple procedure during physical examination has led to the diagnosis of a bronchogenic neoplasm on several occasions, by indicating the presence of a bronchostenosis. Table II will show the number of cases that exhibited these signs (Figure 6).

In addition to the physical signs, the fluoroscopic and roentgenographic findings are important. Here again forced expiration comes into play and when there is an obstructive atelectasis present, one sees the mediastinum shift to the affected side on full inspiration, and also of course, the other x-ray findings of atelectasis. However, these latter need not be present. In the check-valve type of stenosis leading to the obstructive emphysema, one sees a shift to the opposite side on forced expiration and the evidence, at times, of a greater translucency of the affected portion of lung, due to trapped air. However, these may not be noted if there has been infection present and pleural obscuration. Figures 6, 7, 8 and 9 illustrate these points.

Finally, bronchoscopy will often localize the site of the bronchial stenosis and disclose the nature of the obstruction. In addition bronchoscopy may lead to therapeutic cure by the removal of a foreign body, a mucous plug or a calcareous stone.[9,10]

TABLE II

Signs Elicited in the Various Conditions and in the Different Positions with Full Expiration

Bronchogenic Carcinomas	30
Sonorous Rhonchi	4
Sonorous Rhonchi on forced expiration	22
Sonorous Rhonchi lying on affected side	28
Sonorous Rhonchi lying on affected side on forced expiration	30
Lymphoblastoma	3
Sonorous Rhonchi	0
Sonorous Rhonchi on forced expiration	3
Bronchial Adenoma	2
Sonorous Rhonchi	0
Sonorous Rhonchi on full expiration	2
Marked Chondromalacia	2
Sonorous Rhonchi	0
Sonorous Rhonchi on forced expiration	2

Tuberculous cases have been omitted from these figures. All the cases had the signs increased by the lying position. All cases were confirmed by bronchoscopy.

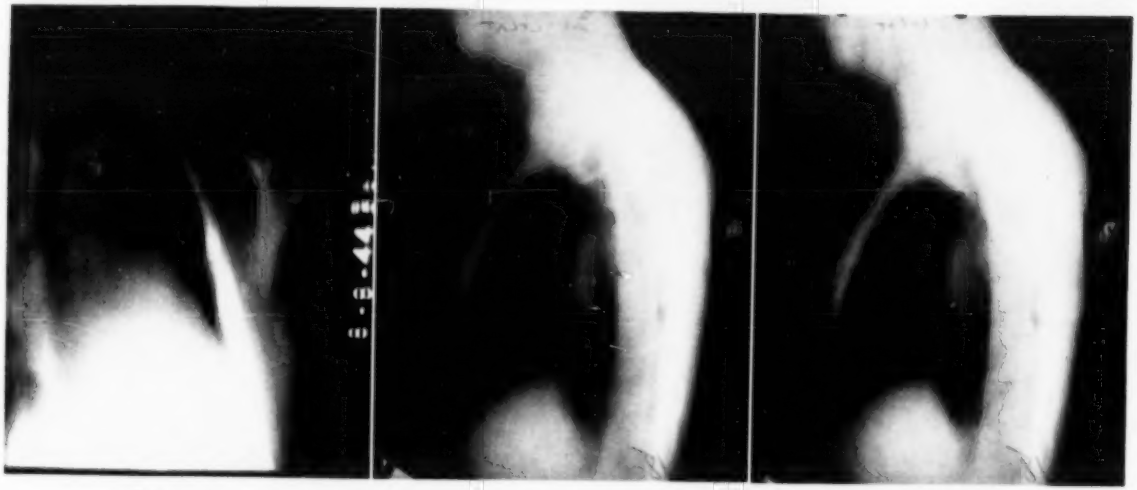

FIGURE 10 FIGURE 11 FIGURE 12

Figure 10: An antero-posterior planigram showing obstruction of the left main bronchus.—*Figure 11:* Lateral planigram revealing the marked narrowing of the main stem bronchus.—*Figure 12:* Lateral planigram at a deeper level still showing the narrowing of the bronchus.

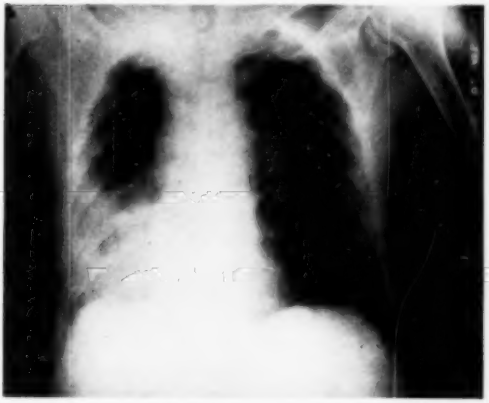

FIGURE 13: Antero-posterior overexposed film showing the narrowing of the right lower lobe bronchus. It can be seen that this is not as clearly visualized as with planigrams.

Bronchography is occasionally resorted to, but ordinarily it is not advised because of the presence of infection and the possibility of aggravating the block. Bronchoscopy is usually the only necessary confirmatory procedure, or in the cases where the obstruction is beyond its reach, tomography or over-exposed films will demonstrate it.

Tomograms are a useful procedure in demonstrating a narrowing of a bronchus. Figures 10, 11 and 12 show the appearance of a narrowed bronchus with the tomographic technique. Both postero-anterior and lateral tomography are of value and both views should be used. A less definite but sometimes easy method of demonstration of a narrowed bronchus is the over-exposed film (Figure 13). This latter method is of much less value than tomography.

CONCLUSION

The presence of sonorous rales, localized to locations of the main bronchial division, which are brought out better or may be elicited only by a forced expiration with the patient lying on the affected side, is pointed out as being a pathognomonic sign of bronchial stenosis. The bronchial stenosis may be due to a variety of pathologic conditions, some intrabronchial, some endobronchial and some extrabronchial. In addition, the methods of fluoroscopy, roentgenography, bronchoscopy, tomograms, and over-exposed films were discussed as to their role in making the diagnosis of bronchial obstruction. The various shifts of the mediastinum were described in both the atelectactic and emphysematous types of bronchial obstruction.

CONCLUSION

La presencia de estetores silbantes, localizados en la división de un bronquio principal que son evidenciados mejor por la espiración forzada con el enfermo yacente sobre el lado afectado, es señalada como signo patognomónico de la estenosis bronquial. La estenosis bronquial puede deberse a varias condiciones patológicas, algunas intrabronquiales y otras extrabronquiales. Además la fluoroscopía, la roentgenografía, la broncoscopía, la tomografía y la radiografía penetrante se discuten en lo referente a su utilidad diagnóstica para la obstrucción bronquial.

Las desviaciones diversas del mediastino se describen tanto en atelectasis como en los tipos enfisematosos de la obstrucción bronquial.

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The Management of Uncontrolled Pulmonary Tuberculosis Complicated by Endobronchial Tuberculosis*

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Endobronchial tuberculosis as a complication of pulmonary tuberculosis has been recognized by pathologists for many years. However, its clinical importance was not appreciated until the last 10 years, and relatively little attention has been paid to the manner in which this complication affects the treatment of the associated parenchymal disease, particularly with artificial pneumothorax and other collapse measures.

Endobronchial tuberculosis is essentially a problem of mechanical obstruction with interference of the bronchial drainage in a patient with pulmonary tuberculosis, and atelectasis, spread of tuberculous disease, pyogenic infection, bronchiectasis and obstructive emphysema are therefore frequent complications of the disease. This may occur in any of three manners, or in a combination of them: (1) through gross obstruction by granulation tissue in the acute phase or by chronic cicatricial fibrostenosis; (2) through partial obstruction accompanied by stagnation of secretions, owing to loss of ciliary action and bronchial peristalsis, and to increased viscosity of sputum; (3) to exaggerated mobility of the bronchial wall, due to localized cartilaginous weakening with probable destruction and producing a check-valve mechanism with resultant trapping of air. In the production of obstruction with stagnation of secretions the following factors are at work: edema and thickening of the mucosa and other layers of the bronchial wall during the acute phase interfere with ciliary action and peristalsis; extensive involvement of mucous gland may decrease mucous formation, thus resulting in increased viscosity of the sputum, making it difficult to raise. Pathologic secretions from the parenchymal disease thus may stagnate at or beyond the disease area in the bronchus.

Since both acute and chronic endobronchial tuberculosis cause obstruction it is fair to assume that the morbid effects from such obstruction depends on the location and size of the involved

*Presented at the 15th Annual Meeting, American College of Chest Physicians, Council on International Affairs, Atlantic City, New Jersey, June 3, 1949. (Read by Title.)

bronchus, as well as on the degree and duration of the obstruction.

The management of uncontrolled parenchymal disease complicated by endobronchial tuberculosis is the most important therapeutic problem and is essentially this: By what method may the parenchymal disease be controlled with the least danger of producing bronchial obstruction and its sequelae?

Some authors have reported good results with pneumothorax, with symptomatic improvement and sputum conversion, but the ultimate outcome of these cases in regard to re-expansion and the status of the pleural cavity were not mentioned. Our own results were poor; from a total of 206 consecutive cases of endobronchial tuberculosis, in 36 patients pneumothorax was used in an effort to control parenchymal disease. Unfavorable complications occurred with great frequency and atelectasis was noted immediately or shortly after induction of pneumothorax in 20 patients (55 per cent) and in 14 of these cases re-expansion was impossible even when attempted early. Sixteen of the total of 36 cases death was due to progressive tuberculosis, including pleural form, or anaerobic infection of the atelectatic lung or a combination of the two, but in all the cases the beginning of the downhill course could be linked with induction of pneumothorax.

Accordingly with our experience I believe the following general plan of therapy may be suggested. Whenever diagnosis of endobronchial tuberculosis having been made, pneumothorax is contraindicated temporarily, and primary attention is paid to the treatment of bronchial lesion. Bed rest, streptomycin, bronchoscopic treatment of the ulcerations and aspiration of secretions are advisable for two reasons: (1) it may do away with the need for collapse therapy; (2) if, after this treatment the parenchymal disease remains a threat to life and collapse therapy is necessary, the bronchial lesion may be healed or become indolent, and under such circumstances the incidence of complications is greatly reduced.

The choice of procedure depend primarily on the character, extension and localization of the bronchial lesion. If the ulceration is minimal and superficial and is located in the main bronchus or, if moderately extensive, has responded readily to local treatment and there is no narrowing of the bronchial lumen, pneumothorax may be used with safety. If ulceration has healed but has left a residual cicatricial stenosis, narrowing the bronchial lumen by 30 or more per cent, pneumothorax generally should not be the procedure of choice because the stenosis indicates a permanently defective bronchial drainage and immediate complications, including atelectasis, are frequent. In these cases,

thoracoplasty offers much better hope from a long-range viewpoint. It will control the parenchymal disease in the majority of cases; it reduces the size of pulmonary bed and reduces to a minimum the danger of late suppuration; and eliminates pleural complications.

These contraindications to pneumothorax should be disregarded only in those patients with minimal parenchymal disease so located as not to be amenable to permanent surgical collapse. Pneumothorax should then be induced only after weighing of the dangers of possible complications against those of the inadequately controlled disease.

If pneumothorax has been induced prior to the diagnosis of bronchial disease the management of the case must depend largely on the clinical course of the patient up to that time. In those patients who develop atelectasis and pleural effusion, one must be careful in re-expanding the lung and if a change of therapy is indicated, it is better to do the thoracoplasty over pneumothorax, than open new areas for supuration through re-expansion. In those patients who fortunately have not developed these serious complications, the safest course seems to be maintenance of pneumothorax with the expectation of an unexpandable lung. In cases with pleural adhesions the general principles recommended above should be applied; if the bronchial lesion is minimal or, if moderately extensive appears indolent and there is no narrowing of the bronchial lumen, pneumonolysis may be performed, provided there are no contra-indications. However, if the bronchial disease is extensive with partial stenosis of the bronchial lumen, and particularly, if there is atelectasis or evidence of retained secretions, pneumonolysis may be harmful and followed by complete obstruction of the bronchus and its serious sequelae.

The occurrence of atelectasis with pneumothorax is due to the presence of air about the root of the lung. This results in interference with normal respiratory motions of the major bronchi in addition with moderate decrease in their size and change in their position. On the other hand, the collapse produced by thoracoplasty is not concentric but is most marked away from the hilum and its effect on the position, the physiologic action, and the functional efficiency of the major bronchi appears to be minimal.

A relatively small number of cases, particularly those with severe fibrostenotic obstruction and pulmonary suppuration, cannot be safely or effectively treated by thoracoplasty, or a good thoracoplasty may already have been performed without producing a satisfactory result. For such patients pulmonary resection constitutes the only effective method of treatment.

SUMMARY

The presence of endobronchial tuberculosis confuses the prognosis and greatly complicates the treatment of the parenchymal lesion. Atelectasis, anaerobic infection, progressive tuberculosis, empyema, and unexpandable lung occur with great frequency when pneumothorax is used. Therefore, pneumothorax should be considered as contraindicated in all but the minimal cases of bronchial tuberculosis, or those patients in whom the bronchial lesion has healed without appreciable stenosis. Thoracoplasty should be the procedure of choice in those patients in whom pneumothorax is contraindicated. In other cases pneumonectomy and lobectomy may be the only chance of restoring health.

RESUMEN

La tuberculosis endobronquial es esencialmente un problema de obstrucción mecanica que interfiere el drenage normal del arbol bronquial, confundiendo el pronostico y haciendo más complicado el tratamiento de la lesion parenquimatosa.

El neumotorax terapeutico lleva con frecuencia en estos casos a complicaciones tales como: atelectasia, infección anaerobica sobreañadida, agravación y progresión de la lesion pulmonar, empiema pleural, pulmon inexpansible, etc.

El neumotorax por lo tanto debe considerarse contraindicado excepto en los casos de tuberculosis bronquial minima sin obstrucción o en aquellos casos en que la lesion bronquial ha curado sin dejar estenosis apreciable.

Parece ser que la toracoplastia es el procedimiento de elección en la mayoria de los casos en que el neumotorax esta contraindicado. En ciertos casos solo la lobectomia o neumonectomia constituyen el unico metodo efectivo de tratamiento.

Acquired Non-Malignant Esophago-Tracheobronchial Communications*

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The development of a communication between the respiratory system and the esophagus invariably leads to characteristic symptoms. The ingestion of fluids is followed by strangling or severe paroxysms of coughing after a momentary asymptomatic pause. In large fistulas solid foods produce the same symptoms and large particles of ingested food may be coughed up. Chronic cough, upper respiratory infections, and repeated attacks of pneumonia are of common occurrence. The fistula may lead to the development of lung abscess or bronchiectasis. Hemoptysis is not an unusual symptom and it may terminate in death.[10] Large fistulas may be associated with severe weight loss. Some patients become accustomed to the inconvenience of the fistula and suffer little interference with nutrition. Many learn the advantage of swallowing in the dorsal recumbent position which tends to minimize the typical paroxysmal attacks of coughing and strangling (Ono's sign[8]). Although these fistulas produce characteristic symptoms, the four cases herein reported were under observation for periods ranging from 10 months to eight years without benefit of a correct diagnosis. The infrequency of the disease has likely led to the lack of correlation of symptoms with the diagnosis of fistula.

We have located in the literature of the past 32 years (1916 to 1949) 75 cases of acquired non-malignant fistulas. Certain pertinent information has been extracted from the 75 case reports which we believe will lead to a more comprehensive knowledge of the subject as well as more defined indications for surgical treatment.

The anatomical relationship of the larynx, trachea and left stem bronchus to the esophagus is conducive to the development of fistulas. At its commencement the esophagus lies in the midline, but it inclines to the left side as far as the thoracic inlet and gradually passes to the midline again at the level of the

*Presented at the Sixth Annual Meeting, Southern Chapter, American College of Chest Physicians, Cincinnati, Ohio, November 14, 1949.

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bifurcation of the trachea. The esophagus lies in immediate contact with the membranous portion of the trachea and the left stem bronchus. This relationship may explain previous observations that malignant and non - malignant esophago - respiratory fistulas more frequently communicate with the left stem bronchus than the right. Our analysis of the reported non-malignant acquired variety has yielded 44 case reports in which the location

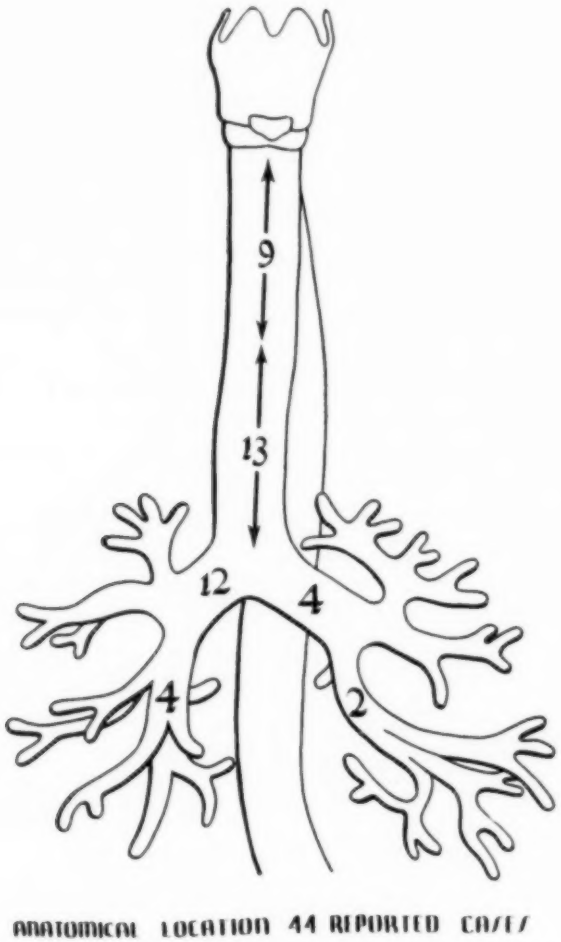

FIGURE 1: Anatomical location of esophago-tracheobronchial fistula in 44 reported cases.

of the fistula was stated (Fig. 1). In this group the right stem bronchus was involved more often than the left. The deep cervical, paratracheal and tracheobronchial groups of lymph nodes lie in immediate contact with the esophagus, trachea, and major bronchi, and may play an important role in the pathogenesis of fistulas of infectious origin.

Etiology

Fifty to 60 per cent of acquired communications between the esophagus and respiratory tract are caused by malignant lesions.[10,12] Acquired non - malignant esophago - respiratory fistulas may best be classified on the basis of etiology (Table 1). In an analysis of 75 reported cases, trauma was found to cause the fistula in approximately one out of three patients (Table 2). The most common causes of traumatic fistulas were respiratory or esophageal foreign bodies, instrumental dilatation of benign strictures of the esophagus and severe crushing wounds of the thorax (Table 3). There seems to be a correlation between the traumatic

TABLE 1

Classification Esophago-Tracheobronchial Fistulas

I. Congenital		
II. Acquired		
A. Malignant		
B. Non-Malignant		
1. Traumatic	a. Foreign body	
	b. Instrumentation	
	c. Wounds of thorax	
	d. Chemical (ingestion caustics)	
2. Esophageal diverticulum		
3. Infection	a. Tuberculosis	
	b. Syphilis (Gumma or aneurysm)	
	c. Fungus	
	d. Non-specific	

TABLE 2

Etiology 75 Reported Cases Esophago-Tracheobronchial Fistula*

Traumatic	21
Undetermined	16
Tuberculosis	14
Diverticulum of Esophagus	11
Syphilis	11
Empyema	1
Actinomycosis	1

*Includes Authors' 4 Cases.

agent and the site of communication of the fistula with the respiratory tree. The fistulas caused by compression injury of the thorax communicated with the trachea in three out of four patients while those caused by foreign bodies and instrumentation of esophageal strictures communicated with either the right or left stem bronchus in seven of eight patients.

Infection was the most common cause of esophago-respiratory fistulas. In a study of the 75 reported cases of non-malignant fistulas, 26 were known to be caused by a specific type of infection (Table 2). Although in 16 additional cases the etiology of the fistula could not be determined by the history, physical findings and frequently by pathologic examination of excised tissue, it seems likely that many of these resulted from pre-existing mediastinal infection of a non-specific character. Tuberculosis and syphilis are the most frequent specific infections which lead to fistula formation. Tuberculosis of the esophagus is a rare disease. We have not observed ulcerative tracheobronchial tuberculosis to lead to fistulous communication with the esophagus in the absence of mediastinal tuberculous lymphadenitis. The pathogenesis of tuberculous fistulas is best explained on the basis of either erosion of caseating or calcified lymph nodes, or rupture of cold abscesses into the tracheobronchial tree and esophagus. Syphilis may involve any part of the respiratory tract or esophagus, and in its tertiary stage may produce fistulas by necrosis and ulceration of gummata. Aneurysms less frequently lead to fistula formation by pressure necrosis.[6] Two case reports of esophago-respiratory fistula caused by actinomycosis appear in the literature.[11,13]

Traction diverticulum of the esophagus was responsible for fistula formation in 11 cases. Although traction diverticula can usually be attributed to pre-existing peri-esophageal infection with subsequent contraction of scar tissue, it is not always possible to identify the initial infection. Traction diverticula may lead to fistulous communication with the respiratory tree by con-

TABLE 3

Etiology 21 Reported Cases Traumatic Esophago-Respiratory Fistula

Foreign Body	4
Dilatation Stricture Esophagus	4
Non-Penetrating Wound	4
Penetrating Wound	2
Operative	2
Chemical (Lye)	1
Incomplete Data	4

tinued activity of the initial infection responsible for the diverticulum, by superimposed secondary infection, and by erosion of calcified lymph nodes. The exact location of the opening of the fistula into the respiratory tree was given in nine of the 11 reported cases of this type. In seven of them the esophagus communicated with a secondary bronchus, usually the lower lobe, and in two the stem bronchus.

Diagnosis

The diagnosis of esophago-respiratory fistula is based upon the history, physical examination, roentgenographic studies and endoscopic examination. Trauma to the chest, ingestion of foreign bodies or caustics, and instrumentation of the esophagus may be followed immediately or later by characteristic symptoms of fistula. Long standing communications between the esophagus and respiratory tree are usually non-malignant. Fistulas of short duration in the cancer age group are suggestive of malignant lesions. If dysphagia precedes the development of symptoms of esophago-respiratory communication, it is indicative of cancer of the esophagus. A fistula of tuberculous origin may be preceded by a protracted and indefinite illness (Case 3).

Physical examination may reveal evidence of tuberculosis, syphilis or mycotic disease. Clinical signs of respiratory tract infection may consist of the presence of moist rales over a lobe or signs of advanced suppurative disease of the lung. Physical signs of pulmonary infection are not always present. A fistula does not invariably lead to chronic suppurative disease of the lung, for the four cases herein reported showed no evidence of permanent changes in the tracheobronchial tree. It is possible to demonstrate the fistula in some cases by detecting the appearance of rales in the lungs after the ingestion of water (Ono's sign[8]). Roentgenographic studies consist of a routine posterior-anterior film of the chest, roentgenograms following the ingestion of contrast media, and bronchograms. Frequently, barium sulfate is administered prior to establishment of the diagnosis; however, ingestion of iodized oil is preferable in that it is less irritating to the tracheobronchial tree. Suitable roentgenograms and fluoroscopy following ingestion of opaque oil will usually delineate the course of the fistulous tract. Esophagoscopy reveals the fistula to lie usually in the anterolateral wall of the esophagus. The opening may be easily overlooked due to its slit-like configuration. A bechic blast can be felt when the tip of the esophagoscope is proximal to the orifice of a large fistula. Biopsy is indicated in papillomatous and ulcerative lesions. Bronchoscopy is of value in confirming the communication of the fistulous tract with the respiratory tract.

TABLE 4: Non-Surgical Treatment 53 Reported Cases Esophago-Tracheobronchial Fistula

	Number of Cases	RESULTS			
		Not Stated	Cured	Unchanged	Died
1. No Specific Treatment	45	27	1	4	13
2. Antiluetic Therapy	7		2	2	3
3. X-ray Therapy	1		1		
TOTAL	53	27	4	6	16

TABLE 5: Surgical Treatment 22 Reported Cases Esophago-Tracheobronchial Fistula

	Number of Cases	RESULTS		
		Cured	Unchanged	Died
1. Cauterization (Endoscopic)*				
A. Chemical	4	3	1	0
B. Electric	1	0	1	0
TOTAL	5	3	2	0
2. Direct Surgical Repair**				
A. With Preliminary Gastrostomy	4	4	0	0
B. Without Preliminary Gastrostomy**	6	5	0	1
TOTAL	10	9	0	1
3. Pulmonary Resection and Closure Esophageal Defect	2	1	0	1
4. Palliative Gastrostomy	3	0	2	1
5. Drainage Coexisting Lung Abscess	2	2	0	0
OVERALL TOTAL	22	15	4	3

*All Small Fistulas. — **Includes Author's 4 Cases.

The opening of the fistula lies in the membranous wall of the trachea or bronchus. It may not be possible to visualize the orifice of the fistula in a secondary bronchus; however, it can be localized by injecting methylene blue solution into the esophagus during bronchoscopy. The colored solution may be observed to well up into the involved segmental bronchus. Bronchiectasis must be excluded by adequate bronchograms as its presence alters the surgical treatment of esophago-respiratory fistulas.

Treatment

Careful analysis of the 75 reported cases of fistula shows that two-thirds of the patients received no specific treatment. In the group of 53 untreated by surgery the outcome was stated in 26; 16 died while hospitalized, six showed no improvement and four were cured (Table 4). The results in 22 cases treated by surgery are extremely gratifying. Fifteen of the 22 were cured, three died and four showed no improvement (Table 5). Only 10 (includes four cases herein reported) of these cases were treated by direct surgical repair,[1-4,7,9] although Poncet[11] established the feasibility of this method in 1896. He successfully closed by curretage and suture through a transtracheal approach in the neck a fistula caused by actinomycosis.

The treatment of traumatic esophago-respiratory fistulas requires consideration of the time interval following injury. Acute traumatic fistulas associated with infection or extensive mediastinal emphysema may require external surgical drainage of the mediastinum. Few patients will be seen sufficiently early to warrant immediate operative closure of the fistula because of diagnostic difficulties and the relatively short period of wound contamination.

Fistulas associated with gummatous ulceration of the esophagus or tracheobronchial tree should receive vigorous antiluetic therapy. If there is proved or presumptive evidence of tuberculosis in a granulating fistulous tract, recent experience suggests that a preliminary course of streptomycin may be of value. Clerf[5] has shown that it is possible to close small fistulas (3 millimeters or less in diameter) by endoscopic cauterization with silver nitrate or sodium hydroxide. Fistulas complicated by bronchiectasis or lung abscess may require pulmonary resection irrespective of the site of communication of the fistula with the tracheobronchial tree. It is always necessary to close the defect in the esophagus whereas the site of communication of the fistula with the respiratory tree may be removed with the resected lobe or lung.

Preoperative preparation of the patient consists of correcting protein depletion, vitamin deficiencies and anemia, and of re-

storing the contracted blood volume. Although serious states of nutritional deficiency may exist, we have not found it necessary or desirable to perform a preliminary gastrostomy. Positive nitrogenous balance can be attained in the patient with a large fistula by means of gastric gavage through an indwelling Levine tube. If necessary, this may be supplemented by parenteral nutritional therapy. A survey is made of the cardiac and renal functions. Preoperatively intramuscular and aerosol penicillin is administered for a period of three or more days. We believe the physical state of the fistulous communication will prove with further experience to be of paramount importance. Smooth epithelized communications are suitable for immediate and direct surgical closure. Small fistulas and those associated with exuberant granulation tissue should receive local cauterization and antibiotics in expectation of cure or alleviation of the local infection preparatory to later surgical treatment.

Caldwell[3] has directed attention to the problems of anesthesia in acquired communications of the esophagus with the respiratory tree. Large fistulas communicating with the trachea are of little concern to the anesthetist providing there is sufficient space for the insertion of an inflatable balloon between the carina below and the fistulous orifice above (Case 4). If the fistula in the terminal trachea does not permit the interposition of a balloon between it and the carina, a snugly fitting intratracheal tube without a balloon will likely prove satisfactory.[3] We have had no difficulty with routine intratracheal intubation anesthesia when the fistula communicated with a stem bronchus or secondary bronchus.

Direct surgical repair of an acquired esophago-respiratory fistula requires a cervical, cervical combined with anterior mediastinal, or transpleural approach. Fistulas located in the region of the superior thoracic aperture require a cervical approach combined with either a median sternotomy (Case 4) or resection of the inner third of the clavicle and the anterior portion of the upper two ribs. The esophagus is mobilized above and below the fistulous communication with the respiratory tree. The fistulous tract is divided and if of sufficient length a portion is excised. The defects in the esophagus and trachea or bronchus are closed by one of the conventional methods of suture. We prefer to close the trachea or bronchus with two layers of interrupted No. 000 silk sutures, a proximal longitudinal mattress suture, and a distal simple on-end suture. The esophageal defect is closed in a transverse plane using two rows of interrupted No. 000 silk sutures. Simple through and through sutures approximate the walls of the defect and the knots are tied within the lumen of the esophagus. The second

layer consists of mattress sutures which approxmiate the muscular wall over the first layer of sutures (Fig. 2). The repaired defects are protected by the interposition of adjacent tissue.

The postoperative care consists of detailed attention to evacuation of tracheobronchial secretions, removal of the intercostal drainage tube in 48 hours (transpleural operation), parenteral penicillin and streptomycin, general supportative measures and fluids by mouth on the seventh postoperative day.

The following case reports demonstrate the successful surgical treatment of four patients with esophago-respiratory fistulas.

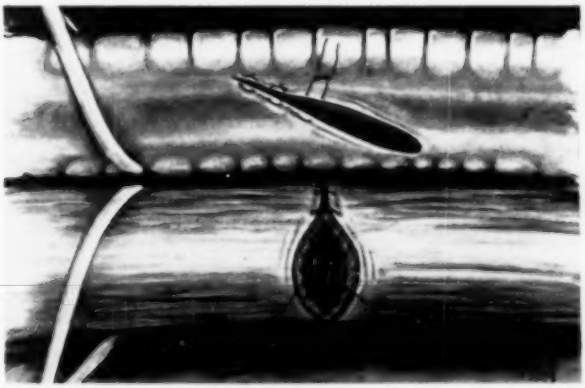

FIGURE 2a

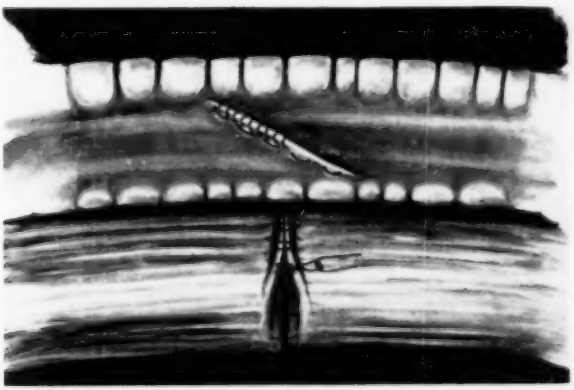

FIGURE 2b

FIGURE 2: Method of closure of defects in esophagus and trachea. (a) First row of sutures. (b) Second row of sutures.

Case 1: During the early part of November 1936, E. J., a white female, 18 years of age, aspirated a small nail. An illness followed characterized by severe coughing attacks, high fever and production of purulent sputum. A diagnosis of pneumonia was made and after a period of two weeks a bronchoscopist was consulted who failed to find the foreign body. An x-ray film at this time showed the nail to lie in the region of the left stem bronchus. Her fever gradually subsided but she continued to cough and one month later a second bronchoscopic examination was carried out. This showed an ulceration on the posterior wall of the left stem bronchus. The foreign body was no longer visible in the roentgenogram. Two months after aspiration of the foreign body she began to cough and strangle on the ingestion of liquids. She suffered from three distinct attacks of pneumonia in the lower lobe of the left lung during the ensuing five years. She had been unable to gain weight but complained little of her symptoms other than strangling and coughing on the ingestion of fluids.

The physical examination revealed an undernourished female who appeared chronically ill. There was suppression of breath sounds at the left base. The hemoglobin was 72 per cent and the red blood cell count was 3,500,000. The total and differential white blood cell counts were normal. The blood serology was negative. A roentgenogram of the chest showed partial obliteration of the left costophrenic sulcus. Bronchoscopic examination revealed a slit-like defect in the left stem bronchus one centimeter below the carina. The fistulous orifice was approximately one centimeter in diameter in its long axis and there was no associated inflammation. Instillation of colored water into the esophagus at the time of bronchoscopy showed a communication to exist between the esophagus and left stem bronchus. Esophagoscopy confirmed the presence of a well epithelized esophago-bronchial fistula. After ingestion of lipiodol an excellent bronchogram was obtained in that the opaque oil readily entered the left stem bronchus. The oil filled both the left and right lower lobes and the bronchial pattern was normal.

On November 12, 1941, a left thoracotomy was performed and the esophagus was mobilized above and below its fistulous communication with the left stem bronchus. A segment of the fistulous tract was excised and the defects in the bronchus and esophagus were both closed with two layers of No. 000 silk sutures. Sulfadiazine was administered for a period of three days preoperatively and for 12 days postoperatively. The pathologist reported, "A tubular structure lined by stratified squamous epithelium."

Her convalescence was uneventful and she was discharged from the hospital on the 21st postoperative day. She has remained entirely asymptomatic and there has been no evidence of recurrence of the fistula during the past seven years.

Comment: A white female, 18 years of age, with a traumatic esophago-bronchial fistula one centimeter in diameter and of five years duration has been cured by resection of the fistulous tract and closure of the esophageal and bronchial defects.

Case 2: W.S., a 46 year old white male had a nine months history of paroxysms of coughing and strangling on ingestion of liquids or solids. In February 1946, he inadvertently swallowed a chicken bone. Seventy-two hours later he noted that the ingestion of liquids or solid food caused

episodes of coughing. The symptoms persisted and three months later he coughed up a chicken bone about one-half inch in length. During the ensuing six months he continued to strangle and cough following ingestion of either liquids or solids, and he was unable to maintain a normal state of nutrition. There was a weight loss of 30 pounds.

The physical examination was not remarkable except for evidence of considerable weight loss and severe malnutrition. Rectal examination showed one plus enlargement of the prostate gland. The hemoglobin was 13 grams and the red blood cell count was 4,200,000. The total and differential white blood cell counts were normal. The sedimentation rate was 27 millimeters the first hour. The blood serology was negative. Roentgenographic study following ingestion of lipiodol showed the presence of a fistulous communication between the esophagus and left stem bronchus. An x-ray film of the chest was normal. Laryngoscopic examination revealed a papilloma of the right vocal cord but both cords exhibited normal function. Bronchoscopy revealed a small patch of granulation tissue on the posterior wall of the left stem bronchus just below the carina. A dilute solution of methylene blue was instilled into the esophagus with the bronchoscope in place and immediately it was observed to appear in the left stem bronchus. A diffuse tracheobronchitis was present and associated muco-purulent secretions were aspirated from the left bronchial tree. The communication with the esophagus could not be identified during esophagoscopy.

The preoperative preparation and observation of this patient extended over a period of three weeks. During this time he was repeatedly observed to cough up large particles of food during his meals. The fistulous communication clinically appeared to be much larger than indicated by bronchoscopic examination. It was necessary to supplement the high caloric, high protein diet by parenteral protein hydrolysates and blood transfusions. Intramuscular and aerosol penicillin was administered for a period of one week preoperatively because of associated tracheobronchitis.

On January 3, 1947, a left thoracotomy was performed through the periosteal bed of the resected fifth rib with the patient under pentothal and endotracheal gas, oxygen and ether anesthesia. The esophagus was mobilized above and below its fistulous communication with the left stem bronchus. The fistula was approximately 3 centimeters in length and 1.5 centimeters in diameter. The fistulous tract was divided between clamps and the defects in the esophagus and membranous portion of the left stem bronchus were both closed by two layers of interrupted No. 000 silk sutures. Bronchoscopy performed immediately after closure of the thorax showed no encroachment on the lumen of the left stem bronchus.

The pathologic examination of the fistulous tract showed it to be well epithelized and lined by squamous epithelium. There was no active inflammation present and no evidence of specific inflammatory disease.

Intramuscular penicillin was administered for a period of 10 days following the operation. On the seventh postoperative day he received fluids by mouth. There were no complications and he was discharged from the hospital on January 22, 1947. He returned for a follow-up examination one month later at which time he was entirely asymptomatic.

Comment: A traumatic esophago-bronchial fistula 1.5 centimeters in diameter in a 46 year old white male has been apparently

cured by resection of the fistulous tract and closure of the esophageal and bronchial defects.

Case 3: E.G. In November 1937, this 65 year old white female had what was thought to be a severe case of "influenza" characterized by low grade fever, ease of fatigue and loss of weight. This ill defined state of health persisted for a period of 18 months. In the early part of 1939 she noticed that ingestion of liquids initiated attacks of coughing and strangling; however, no difficulty was experienced with dry and solid foods. The symptoms showed no marked change until the time of her present hospital admission.

At the age of 43 years she was hospitalized for pulmonary tuberculosis. After a period of six months observation she was discharged with apparently arrested tuberculosis. As a child she had rheumatic fever unattended by complications. Her father died of pulmonary tuberculosis when she was a child.

This patient was an elderly female who appeared to be in good health. The physical examination was essentially negative except for moist rales in the lower lobe of the left lung. The hemoglobin was 80 per cent and the red blood cell count was 3,900,000. The total and differential white blood cell counts were normal. The blood serology was negative. The non-protein nitrogen was 33 milligrams per cent. The kidneys were able to concentrate to a maximum specific gravity of 1.015 during the Mosenthal concentration test. The phenolsulphonephthoalein excretory kidney test was normal. The total serum protein was 7.6 grams per cent with a normal albumin-globulin ratio. The sputum was repeatedly negative for acid fast bacilli. The urinalysis showed one plus albumin with 75 to 100 white blood cells per high powered field. The electrocardiogram revealed abnormal P-waves in leads two and three. The Q-3 and T-3 patterns suggested a residual of old posterior myocardial infarction. The vital lung capacity was 62 per cent of normal.

The preoperative studies and diagnosis in this patient were made by Dr. George A. Welchons, Richmond, Virginia, prior to the patient's hospital admission. A roentgenogram of the chest revealed findings compatible with healed bilateral pulmonary tuberculosis. After the ingestion of a contrast medium, fluoroscopy and suitable roentgenograms demonstrated a fistulous communication of the esophagus with a secondary bronchus of the left lower lobe. The lower lobes of both lungs were filled by the contrast medium and revealed no evidence of bronchial dilatation. The orifice of the fistulous tract could not be identified on bronchoscopic examination. Esophagoscopy showed the orifice of the fistula to be epithelized and to lie in the left anterolateral wall of the esophagus. She was given aerosol and intramuscular penicillin for a period of six days prior to operation.

On November 19, 1947, a left thoracotomy was performed entering the pleural cavity through the periosteal bed of the resected seventh rib. The anesthesia consisted of pentothal and endotracheal gas, oxygen and ether. The upper lobe of the lung was found to be studded with numerous calcified nodules ranging in size from one-half to one centimeter in diameter. There was partial symphysis of the visceral and parietal pleurae. Multiple calcified lymph nodes were encountered adjacent to the bronchi and in the mediastinum. There was a fistulous tract leading from the esophagus to the posterior segmental bronchus of the left lower lobe one centimeter in diameter and four centimeters in length (Fig. 3). The

communication was eradicated by excision of three centimeters of the fistulous tract and closure of the bronchial and esophageal defects as illustrated in Figure 2.

The pathologist reported, "Representative sections display a tubular structure with a central lumen lined by a broad zone of stratified squamous epithelium. The wall exhibits no evidence of an active inflammatory process. No tubercles are persent."

Postoperatively, intramuscular penicillin was administered for a period of ten days. She developed atelectasis of the left lower lobe on the second postoperative day which was promptly relieved by intratracheal catheter aspiration. Seventeen days after operation she was discharged from the hospital. She has had no subsequent cough and no recurrence of symptoms during the past 14 months.

Comment: This 65 year old white female had symptoms of an esophago-bronchial fistula for a period of eight years. Coexisting healed pulmonary tuberculosis and calcification of tracheobronchial lymph nodes are presumptive evidence of the fistula likely being tuberculous in origin, although pathologic examination of the excised fistula showed no tubercles. Excision of the fistulous tract one centimeter in diameter with closure of the esophageal and bronchial defects resulted in an apparent cure.

Case 4: T.M. This 24 year old white male student developed "pneumonia" in August 1944, accompanied by the simultaneous onset of pronounced strangling, choking and coughing on the ingestion of either

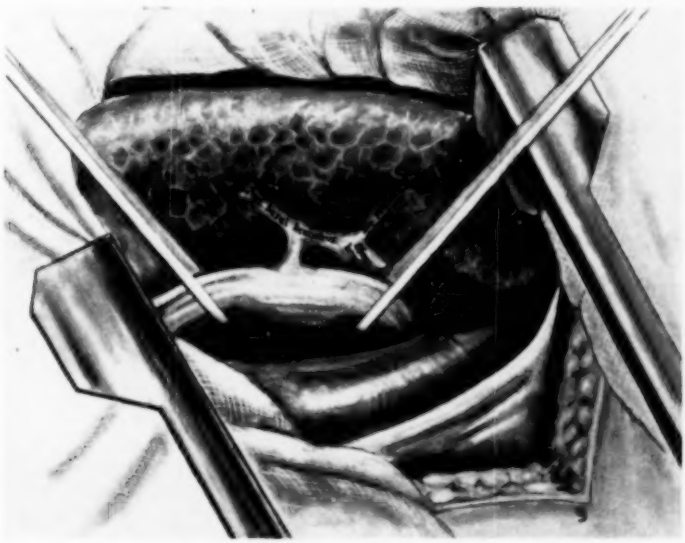

FIGURE 3: Fistulous communication of esophagus with segmental lower lobe bronchus left lung (Case 3).

liquids or solid food. At the onset of the illness he also became hoarse. He recovered from the "pneumonia" after a period of one week but the associated symptoms persisted to the present hospital admission. He suffered from chronic cough unrelated to swallowing and frequently produced blood-streaked sputum. A second episode of pneumonia was experienced several months after the onset of his symptoms. Over a period of four years he had lost a moderate amount of weight even though he had mastered an ingenious method of preventing food from entering the trachea during deglutition. He had noticed that holding his head slightly to the left and leaning backwards led to improved passage of food into the stomach rather than into the trachea.

There was evidence of moderate weight loss. A few transient rales were heard over the bases of both lungs. The physical examination was otherwise negative. The hemoglobin was 15.2 grams and the total and differential white blood cell counts were normal. The sedimentation rate was 21 millimeters the first hour. The blood serology was negative. The first and second strength tuberculin skin tests were negative. The vital capacity was normal. The blood chemistry studies were normal. Roentgenographic studies after the ingestion of lipiodol showed a fistulous com-

FIGURE 4: Ingestion of lipiodol delineates large tracheo-esophageal fistula (Case 4).

munication between the esophagus and trachea at the level of the superior thoracic aperture (Fig. 4). Laryngoscopic examination showed paralysis of the left vocal cord. An ingested silk thread readily entered the trachea by way of the fistula and after being coughed up it was reswallowed. The string made two or three complete revolutions about the described circuit which required its piece-meal removal through a laryngoscope.

Bronchoscopy showed a large fistulous communication of the posterior wall of the trachea with the esophagus at the level of the superior thoracic aperture. The No. 840 bronchoscope could be passed easily into the esophagus by way of the fistulous tract. The fistula had a smooth epithelial lining and appeared to be greater than three centimeters in diameter. The tracheobronchial tree showed severe and generalized purulent tracheobronchitis. Esophagoscopy showed the fistula to lie in the left anterolateral wall of the esophagus 23 centimeters below the upper incisor teeth, and the nine millimeter esophagoscope could be passed through the fistula into the trachea.

The purulent tracheobronchitis required a prolonged preoperative period of aerosol penicillin and streptomycin and intramuscular penicillin. The sputum culture repeatedly showed E. coli. It was possible to maintain his nutritional state by a high caloric, high protein diet; however, he never acquired a positive nitrogenous balance. Preoperative transfusions and parenteral protein hydrolysates supplemented the oral intake.

On September 15, 1948, gas, oxygen and ether anesthesia was administered through a long endotracheal tube. The attached balloon was placed between the fistula above and the carina below. An incision was made from the level of the superior border of the thyroid cartilage to the suprasternal notch along the medial border of the left sternocleidomastoid muscle. The retropharyngeal space was exposed by retracting the sternocleidomastoid muscle and the carotid sheath structures laterally. The cervical approach was not sufficient for exposure of the fistula and the skin incision was extended downward over the mid-sternum to a level just below the third costal cartilage. The sternum was split in the midline and the anterior mediastinum was opened. The exposure was then satisfactory and the esophagus was freed below the fistula by blunt dissection. The left recurrent laryngeal nerve was observed to be incorporated in a mass of scar tissue in the region of the fistula. The cervical esophagus was developed by blunt dissection above the fistula. There was considerable scarring of the mediastinum in and about the fistulous communication of the esophagus with the trachea. The fistula was divided. The defect in the membranous potrion of the trachea measured five centimeters in its greatest diameter and it was closed with two rows of interrupted No. 000 silk sutures. A similar defect in the esophagus was closed in a transverse manner using two rows of No. 000 silk sutures (Fig. 2). The left lobe of the thyroid gland and surrounding scar tissue were sutured over the closed tracheal defect.

Postoperatively, he received two grams of streptomycin daily and 100,000 units of penicillin intramuscularly every three hours. He developed a wound infection complicated by chondritis of the first, second and third costal cartilages on the right. On November 1, 1948, the diseased cartilages were resected and the wound was packed open. The wound required secondary closure. Prior to his discharge bronchoscopy showed no abnormality of the trachea. It was impossible to identify the site of

the healed surgically closed defect. A laryngoscopic examination showed partial return of function of the left vocal cord. Esophagogram showed no esophageal defects.

At the time of discharge on January 18, 1949, he had no cough, no difficulty in swallowing and had gained 25 pounds in weight.

Comment: This 24 year old white male was able to tolerate for a period of four years a fistula which had a diameter of five centimeters. No specific etiologic agent could be demonstrated but there is evidence to suggest that the fistula likely arose from a pre-existing pyogenic mediastinal abscess. The exposure of the fistula at the superior thoracic aperture required a combined cervico-mediastinal approach. Successful closure of the defects in the trachea and esophagus has led to an apparent cure.

SUMMARY

Seventy-five cases of acquired non-malignant esophago-tracheobronchial fistula have been reported in the literature during the past 32 years (1916 to 1949). Analysis of these cases has yielded valuable information.

The fistulas are classified on the basis of etiology. The known causes of fistula formation are infection, trauma and esophageal diverticula. There is a definite correlation between the type of trauma and the location of the fistulous opening in the tracheobronchial tree. Traction diverticula of the esophagus show a high incidence of communication with the secondary bronchi. The most common specific infections leading to fistula formation are tuberculosis and syphilis.

Development of a communication between the respiratory system and esophagus invariably leads to characteristic symptoms. Ingestion of fluids is followed by strangling or severe paroxysms of coughing after a momentary asymptomatic pause. Diagnosis is based upon history, physical examination, roentgenographic studies and endoscopic examinations.

Fistulas associated with active tuberculosis or syphilis should receive antibiotic therapy. Small fistulas and fistulas associated with exuberant granulation tissue should receive local cauterization and antibiotics in expectation of cure or alleviation of the local infection preparatory to later surgical treatment. Those complicated by bronchiectasis or lung abscess frequently require pulmonary resection in addition to closure of the esophageal defect. Smooth epithelized communications unattended by suppurative disease of the lung are suitable for immediate and direct surgical closure.

Four cases of acquired non-malignant esophago-tracheobronchial fistula have been successfully treated by direct surgical

closure. Six cases treated by this method have been reported in the literature during the past 32 years.

RESUMEN

En los últimos 32 años se han referido en la literatura setenta y cinco casos de fístula esófago-traqueobronquial adquirida, no maligna (de 1916 a 1949). El análisis de 3 casos ha proporcionado valiosa información.

Se clasifican las fístulas por su etiología.

Las causas conocidas de fístula son: infección, trauma y divertículo esofágico. Hay una relación definida entre el tipo del trauma y la ubicación de la abertura fistulosa en el árbol bronquial.

La tracción del divertículo del esófago muestra una alta incidencia de comunicación con bronquio secundario. Las infecciones más comunes que conducen a la formación de fístula son la tuberculosis y la sífilis.

El desarrollo de comunicación entre el aparato respiratorio y el esófago invariablemente dan los síntomas característicos.

La ingestión de líquidos es seguida de paroxismos de tos intensos y asfixiantes después de una pausa sintomática momentánea.

El diagnóstico se basa en la historia clínica, examen físico, estudio radiológico y examen endoscópico.

Las fístulas asociadas con tuberculosis activa o sífilis deben recibir tratamiento con antibióticos. Las fístulas pequeñas y las asociadas con granulación exhuberante deben recibir tratamiento local por cauterización y antibióticos en espera de la curación de la infección local para después ser tratadas por cirugía.

Las complicadas con bronquiectasis o absceso pulmonar requieren más a menudo la resección pulmonar además del cierre del orificio esofagiano. Las comunicaciones blandas epitelizadas sin enfermedad suprativa del pulmón pueden tratarse desde luego por cirugía.

Cuatro casos de estas fístulas se han tratado con éxito por cierre quirúrgico directo. Seis casos tratados por este método se han referido en la literatura en los últimos 32 años.

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Generalized Sarcoidosis with Uremia Due to Congenital Single Fused Polycystic Kidney: Necropsy Findings in a Case Previously Reported as Renal Sarcoidosis*

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The purpose of this report is to present the necropsy findings in a patient with sarcoidosis, who died of renal insufficiency. The latter was caused by a single fused polycystic kidney. The renal complications in this patient had been previously ascribed to sarcoidosis of the kidney (Rotenberg and Guggenheim[1]). In a later report by Kleinfelter and Salley,[2] this case was included with three other nonnecropsied cases as examples of renal sarcoidosis simulating glomerulonephritis. Subsequent inclusions of this patient as an example of renal sarcoidosis have appeared in a review of sarcoidosis by Freiman[11] and a review of renal disease by Hall and Luetscher[12] through their references to the earlier papers of Rothenberg and Guggenheim and Kleinfelter and Salley.

It is not within the scope of this report to review the protean manifestations of sarcoidosis. A complete description of the various manifestations of this disease is available in the reviews by Pinner,[3] Rubin and Pinner,[4] Schaumann,[5] Longcope,[6] and Snapper and Pompen[8] and others.

Kraus[9] has shown at necropsy that sarcoidosis may rarely cause a pituitary syndrome. Longcope and Fisher[10] have described cardiac involvement and failure due to sarcoidosis. Small and clinically unimportant sarcoid lesions have been found in the kidneys.[7] However, an extensive search of the literature does not reveal a single death due to renal sarcoidosis proved by postmortem examination .

CASE REPORT

B.K., a 29 year old white male, was in good health until March 1939 when, at the age of 22, he began to cough, expectorate purulent sputum and had temperature elevation. A diagnosis of pneumonia was made. The symptoms subsided and recovery was evidently complete. However, in October 1939 the symptoms recurred. A month later the physical examination disclosed rales throughout both lungs and a friction rub over the right base. X-ray films revealed dense shadows in both hilar

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regions. In April 1940 he was admitted to a hospital and biopsy of an anterior cervical lymph node revealed what was considered to be Hodgkin's disease. On October 11, 1940 he was admitted to the Morrisania City Hospital and at this time the impression was that the patient had sarcoidosis rather than Hodgkin's disease. It was possible to obtain the slides of the original biopsy and the diagnosis of sarcoidosis was confirmed. The blood pressure at this time was 148/100. Repeated intracutaneous tuberculin tests were negative and direct sputum smears for tubercle bacilli were negative. The remainder of the physical examination was negative except for the chest findings, which revealed reticular extension of the process from the hilum into both lung fields.

On January 22, 1941 he was admitted to the National Jewish Hospital in Colorado. The chief complaints at this time were persistent vomiting of two months duration, moderate cough and expectoration of whitish, mucoid material. Nocturia and occasional dysuria were also present. A left epitrochlear lymph node was palpable but there were no other palpable lymph nodes. Roentgen inspection of the chest revealed considerable enlargement of both hila, with extensive nodular and infiltrative changes scattered throughout both lungs, particularly on the right. In the upper mediastinum there was a rounded shadow of large size which projected to the right. X-ray films of the long bones and of the hands and feet were negative. Blood pressure at this time was 154/115.

An electrocardiogram disclosed right axis deviation; sedimentation rate 25 mm. in 60 minutes; in the urine 2 plus albumin, few WBC, and occasional granular and hyaline casts; NPN, 61 mg. per cent; tuberculin test negative up to and including 10 mg. of O.T.; serum calcium, 10.2 mg. per cent and serum phosphorus, 3.1 mg. per cent. Renal function became progressively impaired. The NPN was consistently above 70 mg. per cent. There was a persistent albuminuria and cylindruria, and the specific gravity of the urine was fixed between 1.008 and 1.009. P.S.P. dye excre-

FIGURE 1: Cut section of the single, fused, polycystic kidney demonstrating the numerous cysts, two pelves and the decreased amount of parenchyma.

tion test showed only 9 per cent of dye excreted in 60 minutes. Plasma protein varied from 3.9 to 5 gm. with A-G ratio of from 2.8:1 to 1.1:2. Culture and guinea pig inoculation of sputa were negative for tubercle bacilli.

Biopsy of a left epitrochlear node revealed findings consistent with Boeck's sarcoid. Half of the excised node was ground up and used for guinea pig inoculation with negative results.

The clinical course during the patient's hospitalization in Colorado was as follows: The vomiting subsided within a few months after admission and he gained weight and strength. The hemoglobin rose. The blood pressure remained unchanged.

He was symptom-free and worked as a watchmaker from mid 1943 to the summer of 1945. At this time he found it difficult to work because of easy fatigue, general malaise, dyspnea and some orthopnea. On March 15, 1946 he was admitted to Montefiore Hospital (Service of Dr. Eli H. Rubin) with complaints of orthopnea, dyspnea and cough. Frequent episodes of vomiting had recurred. The family history was negative for tuberculosis.

Physical examination on admission revealed numerous papules, macules and a few slightly raised and non-tender excoriated nodules about the size of a half pea were noted over the posterior and anterior thorax, lumbar area of the spine, and extremities. Fundoscopic examination showed only slight edema of discs on temporal side bilaterally with questionable A-V nicking.

The lungs were normal except for roughened breath sounds, and inspiratory moist rales over the anterior thorax. The heart was enlarged about 3 cm. to the left of the mid-clavicular line on percussion. The rate was 84 per minute, with regular sinus rhythm, except for occasional premature contractions. The B.P. was 170/110, left arm, and 174/110, right arm. Slight tenderness was present over the epigastrium. On abdominal examination only the spleen was palpable, one and a half finger breadths below the costal margin on deep inspiration. The edge

FIGURE 2: Cut section of testes demonstrating several granulomatous lesions on the surface.

was smooth and slightly tender. A left axillary node, about 1 x 2 x 0.5 cm. in size and small inguinal nodes were palpable bilaterally. Two plus edema of the feet and ankles was present bilaterally.

Laboratory examination revealed the following findings: blood urea nitrogen, 154 mg. per cent on admission, dropped to 94.8 mg. per cent two days later, after parenteral fluids, and gradually rose despite treatment to 209 mg. per cent two days before death; blood creatinine gradually increased from 25.1 to 27.5 mg. per cent. Total protein, 7.9 gm. per cent with 5.9 gm. per cent albumin and 2.0 gm. per cent globulin; serum phosphorus, 14.3 and 16.6 mg. per cent; serum calcium, 10.2 mg. per cent; alkaline phosphatase, 4.8 Bodansky units; severe microcytic anemia; Wassermann and Kahn tests were negative; sedimentation rate (Westergreen method), 37 mm. in 60 minutes; ECG, right axis deviation with right ventricular strain. Urinalysis showed a specific gravity of 1.010 to 1.012, 3 to 4 plus albumin and 2-25 WBC HPF. X-ray film of the hands disclosed no pathological bone changes.

Course in hospital: Signs of renal insufficiency progressed with increasing retention of urea and creatinine. A coarse friction rub developed over the left axillary area on March 24, 1946. Edema of the lower extremities became marked and edema of the sacral area and upper extremities appeared on March 28, 1946. At no time did the patient have elevation of temperature. By March 29, 1946 the pleural friction rub had disappeared and occasional rhonchi were heard over the entire chest. A gallop rhythm with a rough mitral systolic murmur appeared. A harsh pericardial friction rub was heard best over the third and fourth left intercostal space just lateral to the sternum shortly before death on March 30, 1946.

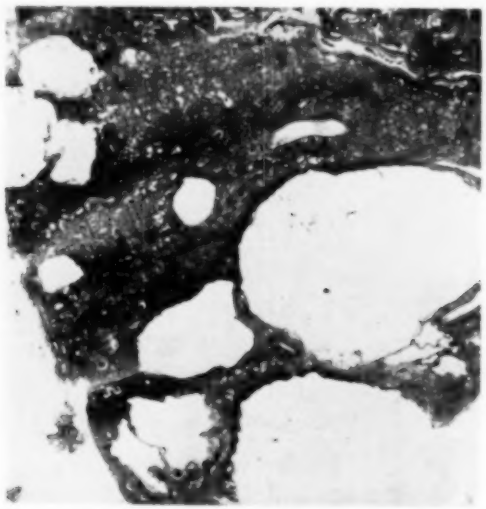

FIGURE 3: Section of kidney revealing the numerous cysts, destruction of parenchyma and metastatic calcification. x Low Power.

Pertinent Necropsy Findings by Dr. Ruth Lubliner

A farily large amount of hemorrhagic fluid was present in the left pleural cavity. The lungs were for the most part non-crepitant. The pleura contained irregularly distributed pinhead to 2 cm. areas of milky white to greyish thickening. Fibrin was present on the posterior and lateral surfaces of the left lung. On cut surface, the parenchyma was dry and greyish-yellow. The interalveolar septa were thickened. In the lower lobes many greyish white streaks were scattered throughout. A few small granular and sligh'ly raised yellowish grey areas, from which thick greyish material could be expressed, were present in the left lower lobe. Greyish-white to chalky white streaks followed the bronchial tree throughout both lower lobes. The hilar, tracheobronchial and mediastinal lymph nodes measured from 1 to 5 cm. in size, the largest ones being in the tracheobronchial group. They were pale grey, moderately firm, and discrete. On section, they were mottled greyish, yellowish and greenish. Many of them were speckled with chalky white spots (evidence of metastatic calcification).

No kidney was present on the right side. The kidney on the left weighed 160 gms. and measured 16 x 6 x 2.5 cm. Its surface was covered with many

FIGURE 4: Section of testis demonstrating the marked disruption of the usual architecture by the fibrotic sarcoid lesions. x Low Power.

small cysts. The kidney was composed of a fused upper and lower part and its capsule stripped with difficulty. Each part of the kidney had a separate pelvis and ureter. The ureters entered the bladder at the normally located ureteral orifices. On section, the parenchyma was markedly decreased by numerous cysts with great distortion of the normal architecture. Scattered throughout the parenchyma were numerous chalky white streaks and spots. On section the testes were sparsely studded with slightly elevated greyish white nodules varying in size from a pinhead to several millimeters.

Microscopic Findings

Lungs: There was widespread chronic pleuritis with a fibrinous pleuritis of the L.L.L. In the L.L.L. and R.U.L. there was chronic pneumonitis. There was also acute pneumonia of the R.U.L. Widespread patchy emphysema was present. Branching bands and areas of dense fibrous tissue were frequently located in perivascular and peribronchial distribution. Numerous foci of calicum deposition were present in the thickened pleura, alveolar septa and bronchial walls. The calcium usually appeared to be deposited around a central, highly refractile, colorless, pale bluish or pale pinkish material. This calcium was sometimes associated with multinucleated giant cells, usually of the foreign body type. The latter sometimes contained the refractile material. Occasionally these lesions contained epithelioid cells and round cells.

Kidney: Marked distortion of the normal architecture was present. There was diffuse fibrosis with extensive focal and diffuse infiltration of cells, chiefly lymphocytes. Numerous calcific deposits of varying size were scattered through the stroma of the cortex and medulla. The parenchymal elements were widely separated by fibrous stroma. There was marked atrophy, degeneration and, in places, necrosis of tubules. Many tubules were dilated, frequently to cystic proportions. Most glomeruli showed partial to complete fibrosis. Arteries and arterioles were moderately sclerotic. Pelvic and peri-pelvic fat contained considerable infiltration of lymphocytes and plasma cells. There was nothing suggestive of sarcoidosis in any lesion.

Testes: There was atrophy of tubules. In lower testes there were several small and large areas of fairly sharply demarcated fibrosis. No epithelhoid nor giant cells were seen in these foci. These areas represented fibrotic sacroid lesions.

Sections of the lymph nodes, lung and spleen stained with the Ziehl-Neelsen method were found not to contain any acid fast bacilli after a 20 minute search in each section. The Von Kossa calcium stain revealed that the calcium deposition was in part associated with the inclusions of the sarcoid lesions and in part due to a metastatic calcification. Gomori's Iron stain revealed bluish iron containing areas present in the calcific foci associated with the sarcoid lesions in the lung, spleen and mediastinal lymph nodes. Bluish staining was also seen in some epithelioid cells and giant cells of the sarcoid lesions. In the kidney, similar blue staining iron salt deposits were seen associated with the calcium.

Anatomical Diagnosis: 1) Sarcoidosis involving lungs, spleen, liver, testes and hilar, tracheo-bronchial, mediastinal, peri-esophageal, perigastric, peri-portal, peri-pancreatic, peri-aortic and left peri-renal lymph nodes. 2) Congential, single, fused, polycystic kidney. 3) Chronic pyelonephritis. 4) Metastatic calcification in lungs, myocardium, lymph

nodes, spleen, mucosa of stomach and kidney. 5) Fibrinous peri-carditis (uremic). 6) Generalized edema. 7) Hemorrhagic pleural effusion and fibrinous pleuritis, left. 8) Chronic pleuritis, bilateral. 9) Chronic pneumonitis, bilateral. 10) Focal pneumonia, right upper lobe.

Comment

This patient was followed over a period of six years and presented a rather typical picture of Boeck's sarcoid without proved skin involvement. At postmortem examination, the lungs, spleen, liver, hilar, tracheo-bronchial, mediastinal, peri-esophageal, periportal, peri-gastric, peri-pancreatic, peri-aortic and left peri-renal lymph nodes plus the testes, were found to be involved. The biopsy of an epitrochlear lymph node in April 1940 revealed typical lesions of sarcoidosis. Even at that time there was beginning fibrosis in areas. Six years later, at the time of death, the lesions were mostly healing or healed. There was, however, still some evidence of exacerbation as shown by cellular granulomata.

The inclusions with deposits of calcium and iron salts were found in the lung, spleen and lymph nodes. There were, however, extensive calcium deposits in those sites not associated with sarcoid lesions. This calcification plus the calcific deposits present in the stomach, kidney and heart can be explained on the basis of metastatic calcification secondary to renal insufficiency.

An extensive search failed to reveal tubercle bacilli.

This patient lived until the age of 29, just over five years after the known onset of renal insufficiency. The basis of the renal insufficiency was the marked decrease of parenchyma due to the encroachment by the numerous cysts. The vascular changes consisting of sclerosis of the arteries and arterioles are not considered to be the primary factor. The chronic pyelonephritis is likewise a secondary factor.

No evidence of sarcoidosis of the kidney was found. Therefore the renal insufficiency previously found[1,2] was erroneously attributed to sarcoidosis. It still remains to be shown that sarcoidosis of the kidney can produce fatal renal insufficiency.

SUMMARY

1) A case of generalized sarcoidosis with a congenital, single, fused, polycystic kidney followed over a period of six years is reported.

2) Death was due to renal insufficiency on the basis of the polycystic disease and chronic pyelonephritis of the single, fused kidney rather than sarcoidosis of the kidney.

3) The renal condition was not suspected during life.

RESUMEN

1) Se presenta un caso de sarcoidosis generalizada, con un riñón poliquístico, fusionado, único y congénito; seguido por espacio de seis años.

2) La muerte fué debida, a la insuficiencia renal, causada por la enfermedad poliquística y a una pielonefritis crónica del riñón único y no a la sarcoidosis del riñón.

3) La lesión del riñón no fué diagnosticada en vida.

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Leuko-Erythroblastic Anemia Due to Bronchogenic Carcinoma

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Standard descriptions of the clinical course and pathology of bronchogenic carcinoma generally are directed toward pulmonary effects and the symptomatology resulting from the more usual visceral metastases. The appearance of a leuko-erythroblastic anemia prior to the above is more unusual. Difficulty is encountered in establishing the etiology of this type of anemia, unless all elements of the differential diagnosis are carefully considered.

Case Report

A 61 year old white male was admitted to the Veterans Administration Hospital, North Little Rock, Arkansas, on March 22, 1949. The complaints were weakness, dyspnea, and pain in the left hip. He had been in fair health until December 1948 at which time the pain developed in the hip. There was a previous history of medical treatment for hypertension and arteriosclerosis. After the onset of the pain in the hip, he fell and struck that side of the pelvis. For this he was treated at another hospital. Laboratory studies showed an anemia and a positive blood serological test for syphilis. Treatment included seven blood transfusions and several injections of some type of antiluetic therapy.

History of primary venereal infection was not obtained and the remainder of the past history was not significant. There were no other complaints.

Physical examination on admission revealed an anemic, seriously ill white male. The skin was pale yellow. Respirations were rapid and shallow. Pulse was 112 per minute and regular. Blood pressure was 110 60. There was mild pharyngitis; elsewhere the mucosae were pale. The pupils were not remarkable. Heart and lungs showed no abnormal changes. There was moderate sclerosis of the peripheral and retinal arteries. The liver was palpated 5 cm. below the right costal margin and the spleen 3.5 cm. below the left costal margin. The lymph nodes were not enlarged. Weakness of the musculature was general and especially prominent in the right lower extremity. The superficial reflexes were diminished on the right; abdominals and cremasterics were absent. Sensory tests were within normal limits.

Laboratory data: On March 23, 1949, there were 2,900,000 erythrocytes per cubic millimeter, 7.5 grams of hemoglobin, hematocrit 28 cc. with mean corpuscular volume 96 and mean corpuscular hemoglobin 26. There

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

were 9,800 leukocytes per cubic millimeter with a differential count of six eosinophiles, two basophils, six juveniles, 14 stabs, 54 polymorphonuclear leukocytes, and 18 lymphocytes. There were 14 nucleated red cells per 100 leukocytes counted. The sedimentation rate was 25 millimeters (corrected), bleeding time six minutes, and coagulation time three minutes. There were 31,900 platelets. The urine was acid, dark yellow, specific gravity 1.020, trace of albumin, negative sugar, and many uric acid crystals. The blood Kahn was four plus, with 10 Kahn units. On March 27, 1949, the total blood proteins were 6.20 grams per cent with 3.70 grams per cent of albumin, and an A/G ratio of 1.48:1; the blood uric acid was 2.2 mg. per cent; non protein nitrogen 58 mg. per cent, icteric index 13.5 units; acid phosphatase 0.14 Bodansky units, alkaline phosphatase 11.62 Bodansky units. Subsequent urinalyses were within normal limits, with no Bence-Jones protein found.

Examination of a specimen of sternal marrow on March 25, 1949, showed the cells to be scarce with some increase in younger forms of the myeloid series.

The cerebrospinal fluid on April 5, 1949, contained five cells, and 73 mg. per cent of protein. The Wassermann was positive, and the colloidal gold curve was 5555432000.

Repeated examinations of the peripheral blood showed variation of the erythrocyte count from 1,640,000 to 2,290,000 cells per cubic millimeter. There was between 4.5 and 5.25 grams of hemoglobin. The leukocyte count gradually rose to 17,500 per cubic millimeter with a continued shift to the left. There was a rise in number of nucleated red cells in the peripheral blood to a maximum of 43 per 100 leukocytes counted on April 15, 1949.

On March 23, 1949, a roentgenogram of the chest showed minimal areas of plate-like atelectasis in the right lung base, with evidence of elongation and tortuosity of the aorta. There was advanced deforming spondylosis of the dorsal spine. On April 4, 1949, examination of the skull and long bones was within normal limits with the exception of minimal sclerotic changes of the right ileum in the region of the acetabulum and in the upper end of the shaft of the right femur near the lesser trochanter.

Treatment included transfusions of 1000 cc. each of whole blood on April 8 and 14, 1949. Penicillin and ferrous sulfate were administered. The patient remained weak and showed no response to the above. There were no chest complaints. The pulse continued weak and rapid. On April 13, 1949, the temperature was elevated for the first time to 99.6 degrees Fahrenheit, and remained between 99 and 100 degrees until death on April 16, 1949.

Autopsy findings: The examination was performed on the day of death. Only the pertinent findings are presented. A small bronchogenic carcinoma was found with diffuse granular gray white involvement of the adjacent parenchyma of the left lung. Similar gray streaks were present in the right lung parenchyma. Enlarged lymph nodes involved by neoplasm were seen in the mediastinum, near the bifurcation of the trachea and in a peribronchial location. A neoplastic nodule was discovered in the left adrenal gland. No other metastases were in evidence. The bone marrow of the ribs was scanty and pale gray. In the vertebrae the marrow was dry, pale, red gray, with no obvious trabeculations.

Other interesting gross findings were numerous small, pale red, friable, irregular vegetations averaging less than two millimeters in diameter on

the mitral valve of the heart. Two similar larger vegetations were on the aortic valve. All had smooth glistening surfaces. The chordae tendinae of the mitral valve were shortened and thickened. In the spleen were several wedge shaped infarcts. The brain weighed 1270 grams and showed atrophy of the convolutions with thinning of the cortex most prominent in the frontal lobes.

Microscopic examination of the lung and bronchus sections showed involvement of the bronchial epithelium and submucosa by neoplasm. There was diffuse invasion of the pulmonary parenchyma. Lymphatics and blood vessels adjacent to the bronchi contained groups of neoplastic cells. There was some involvement of the visceral pleura. The neoplastic cells occurred in groups and strands, with some tendency to gland formation. The nuclei were oval or irregular and hyperchromatic. The cytoplasm was moderate in quantity and pale eosinophilic. There was pleomorphism. Occasional mitotic figures were noted. The larger masses of neoplasm showed areas of necrosis.

A large bronchial lymph node was almost completely replaced by neoplasm with invasion of the adjacent connective tissue. Similar changes were observed in other lymph nodes. Some intravascular groups of neoplastic cells were found in a section of the pancreas. The left adrenal gland showed almost complete replacement by neoplastic tissue. There was marked tendency to glandular arrangement. Considerable necrosis was present, and the neoplastic cells occurred in strands along the cortical cords. There was invasion of the periadrenal adipose tissue.

The marrow sections obtained from rib showed partial to complete replacement of the marrow spaces by neoplastic cells and fibrous tissue. Some bony spicules were intact; others showed osteolytic changes. Hematopoietic tissue was not observed in several rib sections. In the vertebrae there was invasion by neoplastic tissue, fibrosis, and considerable necrosis. Small areas of active erythropoiesis were seen.

Sections of the spleen showed the infarcts. Hematopoietic tissue was not observed here nor in the liver. Cerebral cortical changes were consistent with the clinical diagnosis of paresis.

Comment

In the case presented, the bronchogenic carcinoma was obscured by the absence of respiratory tract symptoms. The admission examination suggested an anemia. Investigation of this disclosed a leuko-erythroblastic anemia. Further investigation for possible etiological factors failed to incriminate the lungs or other sites of primary malignancy and the tentative clinical diagnosis was myelofibrosis.

The appearance of an anemia with not only a large number of circulating nucleated red cells in the peripheral blood, but also an increase in immature forms of the myeloid series suggests a space occupying disorder of the bone marrow. Differential diagnoses should include metastatic carcinoma to bone marrow, multiple myeloma, myelosclerosis, Albers-Schonberg disease, and various disorders of the reticulo-endothelial system.

The common factor to these various diseases appears to be some

degree of loss or replacement of marrow from neoplastic invasion, necrosis, fibrosis, or other degenerations. The blood picture resulting from these pathological changes shows features other than those expected alone from destruction of marrow. Some cases show areas of active erythropoiesis adjacent to masses of carcinoma cells or regions of necrosis of marrow. Some degree of marrow stimulation appears to be present in leuko-erythroblastic anemia. There is discussion of the effect of toxicity of the various diseases on the marrow causing both a stimulation as well as destruction; another suggestion has been the loss of essential nutrients to the marrow due to the presence of the neoplastic cells.

Metastatic carcinoma appears to be the most frequent of the etiological factors in production of leuko-erythroblastic anemia. Primary malignancies should be searched for in the various organs, particularly in the prostate, breast, lungs, thyroid, kidneys, adrenals, and gastrointestinal tract. Bone marrow studies often offer aid in establishing the diagnosis.

Bronchogenic carcinoma is notorious for its ability to metastasize widely. Nevertheless, it is unusual to find the blood changes of a leukoerythroblastic anemia before the primary neoplasm or some of the other visceral metastases. In this case, the positions of the primary neoplasm and metastases to organs other than the reticuloendothelial system were not obvious clinically, nor even after studies of the blood and marrow. The absence of any respiratory signs or symptoms was particularly important and failed to provide a lead for further diagnostic studies in this system.

Pathologically this case is of interest in that the tendency to glandular arrangement of the neoplastic cells was more apparent in the metastases than in the lung. No evidence of myeloid metaplasia was found in the liver, spleen, or other organs. Splenomegaly was due to infarcts associated with an endocarditis. The marrow showed degenerative changes due to neoplastic infiltrates, and there was considerable necrosis and fibrosis.

CONCLUSIONS

1) A case of bronchogenic carcinoma is discussed in which leuko-erythroblastic anemia was the most important clinical finding. 2) Differential diagnosis of this type of anemia is discussed.

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Bronchogenic Carcinoma

A Clinicopathologic Study of Fifty Autopsied Cases

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Fifty cases of bronchogenic carcinoma proved by autopsy were observed at the Letterman General Hospital, Presidio of San Francisco, California, between January 1, 1920 and December 31, 1948. Among the 3,001 autopsies performed during this period the diagnosis of bronchogenic carcinoma was established in 59 instances, but data on nine cases were too scanty for the purposes of this analysis. A correlation of the clinical and postmortem observations in the 50 cases has been attempted and the morphologic features of the tumor in each case have been reviewed. Three main histologic types were recognized: squamous cell, small cell, and adenocarcinoma.

Incidence

Of the 3,001 cases on which autopsy was performed from January 1, 1920 to December 31, 1948, 845 (21.5 per cent) revealed malignant lesions of various types. The 59 cases of carcinoma of the lung constituted 1.9 per cent of all autopsies and 7.0 per cent of all malignant tumors diagnosed postmortem.

The relative increase in carcinoma of the lung noted within recent years appears to be corroborated in our small series, as shown in Table 1. In the decade 1920-1929 the percentage of bronchogenic tumors in autopsy material was 1.2 per cent; from 1940 through 1948, it was 2.7. Carcinoma of the lung was fourth highest in incidence among the malignant tumors observed, carcinoma of the stomach being first, lymphoma and leukemia second, and tumors of the large bowel third. The large number of cases of lymphoma and leukemia may be explained by the fact that these are diseases of the younger age groups, and individuals of military age constitute the majority of the population at Letterman Hospital. All patients dying from bronchogenic carcinoma were white and 92 per cent were males, but this high percentage may reflect the predominately male personnel of the Armed Forces. However, in 1,214 cases collected from recent litera-

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ture the sex incidence is comparable, 1,059 or 87.2 per cent being males (Bjork, Maher, Horn, Halpert, Brindley, Craver, Tenzel, Corsello, Mitton, Mulligan and Lindskog).

The youngest patient in our series was 26 years of age and the oldest 75. The average age of patients with squamous cell carcinoma was 55.4 years, with small cell carcinoma, 52.0 years, and with adenocarcinoma, 48.5 years. The analysis of the incidence in age groups of the entire series is compared with a similar analysis of 931 cases in the literature in Table 2. It will be noted that 74 per cent of the cases in our series occur in the age group of 40 to 69, as compared to 86.3 per cent in the collected series, a difference also explainable on the basis of the hospital population.

Etiology

Various factors which presumably influence the development of bronchogenic carcinoma have been suggested in the literature, but the only one proved to have such an effect is the inhalation of radium emanating substances. In this analysis no factor was ap-

TABLE 1

Malignant Tumors and Carcinoma of Lung Among Autopsies at Letterman General Hospital by Decade, 1920-1948.

Decade	Autopsies	Malignant Disease	Carcinoma of Lung	Percentage Carcinoma of Lung of Total Autopsies
1920-1929	765	162	9	1.2
1930-1939	1210	352	22	1.8
1940-1948	1025	331	28	2.7

TABLE 2

Classification of Bronchogenic Tumor in Relation to Age Group Bronchogenic Carcinoma

Age	Squamous Cell	Small Cell	Adeno-carcinoma	Total	Recorded Cases of Malignant Tumor
Under 20					7
20-29		1		1	13
30-39	1	2	3	6	76
40-49	5	7	1	13	258
50-59	9	3	3	15	371
60-69	3	5	1	9	175
Over 70	4	2		6	29
TOTAL	22	20	8	50	929

Source: Autopsies at Letterman General Hospital, 1920-1948.

parent which had any significant etiologic relationship to the development of bronchogenic carcinoma. Among the patients were persons from all sections of the country and from all walks of life, many of whom were widely traveled. Their occupations are listed in Table 3. One patient, a mill-worker, was constantly exposed to ore and rock dust, and two firemen and one refrigeration engineer were occasionally exposed to irritating gases; otherwise, occupation seemed to play no important role.

Duration of the Disease

The duration of the disease in each case was computed from the time of onset of the first symptoms of the illness which led to death. The duration of illness for patients with squamous cell tumor was 13.6 months, for the small cell type, 5.6 months, and

TABLE 3

Occupations of 50 Patients Dying of Bronchogenic Carcinoma

Occupation	Squamous Cell	Small Cell	Adeno-carcinoma	Total
Enlisted Personnel, U. S. Army	5	4	1	10
Officer, U. S. Army	4	3	1	8
Salesman	2			2
Tavern Keeper	2			2
Housewife	1	2	1	4
Mechanic	1	2		3
Machinist	1			1
Red Cross Worker	1			1
Janitor	1			1
Carpenter	1			1
Campaign Director	1			1
Officer, U. S. Navy	1			1
Ore-Mill worker	1			1
Fireman		2		2
Electrician		1		1
Refrigeration Engineer		1		1
Steel worker		1		1
Attorney		1		1
Purser, Merchant Marine		1		1
Lumberman			1	1
Painter			1	1
Not Stated		2	3	5
TOTAL	22	20	8	50

Source: Autopsies performed at Letterman General Hospital, 1920-1948.

for adenocarcinoma, 21.5 months. The average duration for all types was 11.7 months.

Clinical Findings

Symptoms: The first symptoms in each case are presented in Table 4 with comparative data in 653 cases collected from the recent literature (Bjork, Maher, Hollingsworth, Corsello).

In this series, as in other reported series, cough was most frequently the first symptom. This cough was dry, persistent and

TABLE 4

Symptoms of Bronchogenic Carcinoma
(50 Cases from Letterman General Hospital, 1920-1948)

First Symptoms	Cell Squamous	Small Cell	Adeno-carcinoma	Total	Per cent	653 Collected	
						No. Cases	Per cent
Cough	9	8	3	20	40	332	50.8
URI and Chest Infections		1	1	2	4	96	14.6
Chest Pain		3	1	4	8	96	14.6
Hemoptysis						53	8.1
Dyspnea		1*		1	2	45	6.9
Weakness and Lassitude	2	3		5	10	44	6.8
Loss of Weight	4	3		7	14	18	2.7
Metastases						10	1.5
Expectoration		1*		1	2	8	1.2
Pain in Other Parts				5	10	7	1.1
Back Pain	2			(2)			
Shoulder Pain	1	1		(2)			
Upper abdominal Pain	1			(1)			
Hoarseness	2			2	4	7	1.1
Headache						4	
Fever						2	
Wheeze						1	
Convulsions						1	
Pleural effusion	1			1	2	0	
Swelling of feet and ankles	1*			1	2	0	
Night sweats	1*		1	2	4	0	
Cervical nodes			1	1	2	0	
Chest tightness		1		1	2	0	

*Appeared simultaneously with other symptoms.

irritating, or it was superimposed upon a long-standing cough, changing its character suddenly or gradually. The cough usually was aggravated when the patient was lying down. When the cough was productive, the sputum was thin and nonpurulent for a relatively long time before it became purulent. Hemoptysis did not accompany the cough as a first symptom but was one of the first three symptoms in approximately 20 per cent of cases.

Loss of weight was the second most frequent early symptom. An average loss of 14 pounds was recorded for patients first presenting themselves for treatment.

Weakness and lassitude were complaints in one-third of the cases. However, more recent experience would indicate that weakness, easy fatigability, and lassitude are much more frequent early symptoms, and it is believed that if patients were closely ques-

TABLE 5

Frequency of Symptoms in 50 Cases of Bronchogenic Carcinoma

All Symptoms	Cases	Per cent
Cough	47	94
Weight loss	40	80
Sputum	30	60
Chest pain	28	56
Dyspnea	23	46
Hemoptysis	18	36
Weakness and fatigue	16	32
Shoulder pain	14	28
Hoarseness	11	22
Back pain	9	18
Repeated URI	7	14
Dysphagia	6	12
Upper abdominal pain	5	10
Night sweats	4	8
Chest tightness	4	8
Lump in axilla	3	6
Lower abdominal pain	2	4
Abdominal mass	2	4
Paraplegia	2	4
Wheeze	2	4
Cervical nodes	2	4
Pleural effusion	1	2
Swelling of feet and ankles	1	2
Fever	1	2
Jaundice	1	2
Sore throat	1	2
Hematuria	1	2
Palpitation	1	2
Convulsions	1	2

Source: Autopsies, Letterman General Hospital, 1920-1948.

tioned, it would be found that these vague symptoms are among the first. Profound changes of this nature, however, are late symptoms.

Chest pain was a presenting symptom in only 8 of our cases and usually occurred late in the disease. It was dull, boring, and continuous, tended to be worse at night, and was frequently referred to the back or the right upper abdominal quadrant. In many cases the first complaint was pain in either shoulder or the back. Hoarseness was a late symptom in all cases, and dysphagia was found to be a terminal event in virtually all cases. All symptoms which occurred during the course of the disease are listed in Table 5.

Physical Findings and Clinical Examinations

Table 6 summarizes the physical findings and basic laboratory tests on admission. The disease was well advanced in the great majority of the cases. However, it should be noted that until January 1946, patients thought suitable for pneumonectomy were

TABLE 6

Relation of Physical Findings and Laboratory Data to Type of Bronchogenic Carcinoma.

Physical Findings	Adeno-carcinoma	Squamous Cell	Small Cell	Total
Consolidation:				
Increased B.S.		1	1	2
Decreased B.S.	3	11	12	26
Pleural effusion		1		1
Rales	3	4	3	10
Negative chest	1	10	4	15
Wheeze		1		1
Paralysis of vocal cord		1	2	3
Friction rub			1	1
Diminished diaphragmatic movements			1	1
Atelectasis and mediastinal shift			1	1
Supraclavicular mass			2	2
Edema of chest wall	1			1
Fever	3	12	12	27
Laboratory Data:				
Leukocyte count (Over 8500)	4	16	19	39
Hemoglobin (Below 70%)	2	15	7	24

Source: Autopsies, Letterman General Hospital, 1920-1948.

TABLE 7

Roentgen Observations in 50 cases of Bronchogenic Carcinoma in Relation to Type of Tumor.

	Squamous Cell	Small Cell	Adeno-carcinoma	Total	Per cent
Parenchymal opacities				34	68
With atelectasis	(15)	(4)		(19)	(38)
Without atelectasis	(4)	(7)	(4)	(15)	(30)
Hilar enlargement	2	1	1	4	8
Atelectasis				8	16
Massive	(1)	(2)		(3)	(6)
Lobar	(2)	(1)		(3)	(6)
Partial	(2)			(2)	(4)
Emphysema				0	
Narrowing of rib spaces	1	2		3	6
Shift of mediastinum	1	2		3	6
Elevation of diaphragm	5	3		8	16
Cavitation	2	1		3	6
Flocculent densities				1	2
Unilateral				(0)	
Bilateral	(1)			(1)	(2)
Pleural effusion	3	6	1	10	20
Old fibrosis in part of one lobe		1	1	2	4
Mottling			1	1	2
Infiltration		3	2	5	10
Infiltration interpreted as lobar pneumonia	4			4	8
Spherical or nodular densities				4	8
Unilateral	(3)			(3)	(6)
Bilateral	(1)			(1)	(2)
*Osteolytic lesions	6 cases	2 cases	0	8	16
Femur	(1)	(1) (upper)			
Ulna	(1)				
Humerus	(1)				
Ribs	(2)	(1)			
Skull	(1)				
Vertebrae (cervical)	(1)				
Ileum	(1)				
Scapula		(2)			
No x-rays		1		1	2

*Figures opposite osteolytic lesions indicate number of cases. The 12 lesions listed occurred in these cases.

Source: Autopsies, Letterman General Hospital, 1920-1948.

transferred to the Army Thoracic Surgery Center at Fitzsimons General Hospital and do not appear in this series. The physical signs most often present were dullness to percussion and decreased breath sounds, suggesting consolidation, pleural effusion, or atelectasis. Fever occurred during the course of the disease in approximately one-half of the cases. The total leukocyte count in most cases exceeded 8,500. Hemoglobin readings below 70 were common. Smears for acid-fast bacilli were made on repeated occasions in eight of the 50 cases; all were negative for organisms.

Roentgen Findings

Abnormal roentgen findings were present on admission in a high percentage of cases. Roentgenograms of the chest were taken in 49 cases and abnormalities were apparent in all except one. Localized emphysema, which has been described in the literature as an early manifestation, was noted. In 68 per cent of the cases definite opacities were visible in the lung fields, and pleural effusion was present in 20 per cent. These opacities were more frequently seen in cases of squamous cell carcinoma, and pleural effusion was most often associated with the small cell carcinoma.

Diagnosis

The diagnosis was correctly made within three weeks of admission to the hospital in 29 cases (58 per cent) and incorrectly in 21 (42 per cent). The incorrect diagnoses are listed in Table 8.

TABLE 8

Incorrect Diagnoses in Relation to the Type of Tumor in 21 Cases of Bronchogenic Carcinoma.

Incorrect Diagnoses	Squamous Cell	Small Cell	Adeno-carcinoma	Total
Tuberculosis	2	1		3
Pneumonia	2	1		3
Bronchiectasis		1		1
Lung abscess	1			1
Gastric carcinoma	1	2		3
Mediastinal tumor		2		2
Malignancy, primary site unknown	1	2		3
Bronchial cleft carcinoma	1			1
Carcinoma of pelvis of the kidney with metastases	1			1
Malignant lymphoma			2	2
Pernicious anemia			1	1
TOTAL	9	9	3	21

It will be noted that errors occurred in approximately the same proportion in each of the three types of bronchogenic carcinoma. Tuberculosis and nonspecific pulmonary infections were the mistaken diagnoses most frequently encountered. In a number of instances the lesion was thought to be metastatic to the lung, and in certain others the physician seemed to have been reluctant to make a diagnosis of bronchogenic carcinoma.

Diagnostic procedures other than roentgenography included bronchoscopy which was performed on 11 patients with positive results in six. Lymph node biopsy confirmed the clinical diagnosis six times and was negative once. Thoracotomy was undertaken four times resulting in a positive diagnosis in every case. Examination of the sediment of the pleural fluid revealed the true nature of the lesion in three cases out of nine. Biopsy of a metastatic lesion yielded a correct diagnosis in two cases and a diagnosis of a different and incorrect tumor in two additional cases. Bronchial smears prepared and stained by the Papanicolaou technique were done in two cases and the diagnosis of carcinoma made in both.

Delay in Diagnosis

Despite all diagnostic facilities available, there was a considerable delay between the onset of symptoms and establishing the diagnosis. The average delay was found to be 7.5 months. The patients' delay accounted for 6.0 months in all cases, and the physicians' delay in diagnosis, for 1.5 months. In the squamous cell group, patients' and physicians' delay averaged 7.6 and 1.6, respectively; in the adenocarcinoma group, 7.7 and 1.3, respectively; and the small cell group, 3.7 and 1.4 months respectively.

Pathology

Formalin-fixed, hematoxylin and eosin stained sections from the primary sites and metastatic lesions were reviewed in all cases in this series. For the purposes of this discussion the 50 cases were divided as to cellular type: squamous cell, small cell, and adenocarcinoma. The squamous group predominated with 22 cases (44 per cent), the small cell carcinoma was next with 20 cases (40 per cent), and the adenocarcinoma was the smallest group with eight cases (16 per cent). In general, there was minimal admixture of the major tumor types in the individual case, only three (6 per cent) showing significant admixture. One of these, a small cell carcinoma, displayed differentiation to adenocarcinoma in several of its metastases, with the presence of cuboidal and columnar cells having a moderate amount of cytoplasm and a tendency to formation of acini. Minimal squamous differentiation was observed

in one of the metastatic foci of a small cell carcinoma, and one squamous carcinoma showed a definite small cell character in one metastasis to a lymph node.

The location of the primary tumor in seven of the 50 cases had not been adequately defined; therefore, the following percentages as to origin are based on 43 cases with full data. The greater number of tumors arose centrally, 78 per cent either in the main stem bronchi or in the immediately adjoining primary lobe bronchi (epiarterial and hyparterial branches). Secondary branch bronchi were the site of origin in seven per cent of the cases, and the remaining 15 per cent were described as diffuse, with no primary site or alteration of bronchial mucosa evident.

TABLE 9

Site of Origin of 50 Bronchogenic Tumors

Type	Main Stem	Primary Bronchi	Secondary Bronchi	Diffuse, No Focality	Insufficiently Described for Localization	Total Cases
Squamous Cell	6	8	3	3	2	22
Small Cell	7	9	0	1	3	20
Adeno-carcinoma	1	3	0	2	2	8
TOTALS	14	20	3	6	7	50

Source: Autopsies, Letterman General Hospital, 1920-1948.

The tumors were almost equally distributed between the lungs, 46 per cent arising in the right, 48 per cent in the left; one was bilateral and diffuse, and the localization of two was not given in the gross description. The upper lobe of the right lung was most frequently involved, followed by the upper and then the lower lobes of the left lung. In 60 per cent of the cases the tumor arose in either of the upper lobes; in 40 per cent, in the lower lobes. The middle lobe was not primarily involved in any case in this series. The main stem bronchus was the site of origin for 35 per cent of the small cell tumors, for 27 per cent of the squamous carcinomas, and for 12 per cent of the adenocarcinomas.

Complications common to all bronchogenic carcinomas studied included: bronchial occlusion, bronchiectasis, extension of tumor to chest wall, and pleural and pericardial effusion. Partial to complete occlusion of the bronchus in which the tumor originated was found in 68 per cent of the cases, occurring with about equal frequency in the squamous and small cell types, but relatively seldom in the adenocarcinomas. Bronchiectasis was described in almost one-half of the cases, and was most frequently associated

with squamous cell carcinoma. Extension of the tumor to the chest wall was noted in one-fourth of the cases, almost equally distributed among the three tumor types. Pleural effusion was present in about one-half of the cases, 63 per cent of these effusions being hemorrhagic. Pericardial involvement was found in one-fourth of the group (13 cases), the majority showing an associated hemorrhagic pericardial effusion; the minority, fibrinous pericarditis without effusion. Tumor was demonstrable in sections of myocardium or pericardium in almost three-fourths of the cases with pericardial involvement.

Squamous Cell Tumors: Gross Features: In 44 per cent of the cases the tumors were of the squamous cell type. Almost half of these originated in primary lobe bronchi in the hilar region (epiarterial and hyparterial branches), and approximately one-third originated from the main stem bronchi. The remainder originated either from secondary branch bronchi or were without evident bronchial localization. Slightly more of the squamous cell tumors arose in the right lung than in the left, and more were primary in the right upper lobe than in any other single lobe;

TABLE 10

Location of Tumor in 50 Cases of Bronchogenic Carcinoma

Type	RUL	RML	RLL	LUL	LLL	Main Stem Origin	Insufficiently Described for Localization	Total
Squamous Cell	5	0	4	2	3	6	2	22
Small Cell	3	0	0	4	3	7	3	20
Adeno-carcinoma	1	0	0	2	1	1	3	8
TOTAL	9	0	4	8	7	14	8	50

Source: Autopsies, Letterman General Hospital, 1920-1948.

TABLE 11

Pleural Effusion in 50 Cases of Bronchogenic Carcinoma

Type	Total Cases	Hemorrhagic Effusion	Serous Effusion	Per cent
Squamous Cell	22	3	2	22
Small Cell	20	6	4	50
Adenocarcinoma	8	5	2	87
TOTAL	50	14	8	44

Source: Autopsies, Letterman General Hospital, 1920-1948.

the least frequent primary site was the left upper lobe (Tables 9 and 10). In general, bronchiectasis, abscess formation, large intrapulmonary tumor masses and central necrosis were relatively more frequent in cases of squamous cell carcinoma than in either small cell carcinoma or adenocarcinoma. Bronchiectasis was present in one-half of the cases of squamous cell type in comparison to an incidence of one-third in cases of the other two types. Intrapulmonary tumor masses, measuring from 3.0 to 10.0 cms., were found in slightly more than one-third of the 22 cases and almost invariably displayed central tumor necrosis and abscess formation. Another feature was the greater incidence of tumorous involvement of the chest wall observed in more than one-third of the cases, compared with an incidence of one-fourth and one-fifth, respectively, in the adenocarcinoma and small cell types.

Histologic Features: The squamous carcinoma cells, as a rule, were grouped in nests, sheets, and columns and were of polyhedral or pavement type. About one-fourth of the cases show focal areas in which these characteristic cells were mixed with cuboidal or spindle cells. In general, the histologic features of the metastatic lesions were similar to those of the primary tumor. In some instances, the metastases in liver and adrenal contained cells of more varied sizes and a greater number of tumor giant cells than the primary pulmonary tumor. In most of the cases it was possible to see at least one of the criteria of squamous differentiation: prickles, kerato-hyaline material, central whorling or pearl formation. All of these features could be observed in half of the cases, and in most of the remainder either intercellular bridges or kerato-hyaline material were demonstrable. These differential features were lacking in only four of the 22 cases of squamous cell tumor, and in these the diagnosis was based on the presence of moderate to large polyhedral or pavement cells with relatively abundant cytoplasm, and on the absence of acinar formation and mucin production.

The accompanying stroma tended to be relatively scant in almost all cases; very rarely did a tumor display prominent desmoplastic properties. Vascularity was relatively minimal in the squamous group. Necrosis of tumor was a more variable feature, moderate in the majority and marked in about one-fourth.

The nuclei were oval and irregularly shaped. The proportion of darker staining and hyperchromatic nuclei to the vesicular type with finely divided chromatin granules was variable, but usually there was a preponderance of the vesicular type. In only a few of the tumors were nuclei of the two types in equal proportions. Distinct nucleoli were noted in all but one case, but in general they were not as prominent as in the adenocarcinomas. Some of

the squamous tumor cells showed multiple nucleoli. Mitotic figures were minimal to moderate in number, usually minimal. In only one case were mitoses numerous, and then they were noted in the metastases rather than in the primary focus. Tumor giant cells, hyperchromatic and often multinucleated, were a rather prominent feature in over one-half of the cases.

In approximately one-half of the cases of the squamous type tumor cells were noted in either lymphatic channels or blood vessels in sections from the primary lung sites. In correlating the presence of tumor cells in blood channels with metastases to distant organs (metastases to kidneys, adrenals, brain, and bones other than those of the thoracic cage are most likely to be blood borne), tumor cells were demonstrated within blood channels in sections from the primary lung site in eight of 11 cases with metastases of the hematogenous type, thus permitting a positive correlation in 72 per cent. From the opposite approach, in only one of ten cases which showed no metastases of the hematogenous type, were tumor cells demonstrated within the lumina of blood vessels in sections from the primary site.

Small Cell Carcinoma: Gross Features: In 40 per cent of the cases studied, the primary tumor was small cell carcinoma. Origin in the main stem bronchus was established in 41 per cent of these, representing a higher incidence than for either squamous cell carcinoma or adenocarcinoma. The remainder originated in the primary lobe bronchi (epiarterial or hyparterial branches), except one which was described as diffuse. In general, central or hilar origin was observed in cases of this group more often than in those of the squamous variety. When small cell carcinoma originated in primary lobe bronchi, origin in the left upper lobe predominated. The primary tumor arose with almost equal frequency in the right and left lung, the left side leading by a slight margin. Bronchiectasis was less often associated with tumors of this type than with squamous cell carcinoma (35 per cent as compared with 50 per cent), but involvement of the chest wall was observed in about the same frequency. Associated pleural effusions were observed twice as frequently with small cell as with squamous cell carcinoma, and superior mediastinal masses three times as often. There was no appreciable difference between the incidence of tumor involvement of the heart and pericardial effusions in the small cell and squamous types. There was a greater incidence of encirclement and encasement of the aorta and superior vena cava by the small cell carcinoma.

Histologic Features: In general, the small cell carcinomas consisted of rather uniform-sized tumor cells growing in narrow to moderately wide anastomosing columns and cords and in alveolar

nests. Palisading of tumor cells was frequently noted about blood vessels, and the tumor tissue was most compact and viable-appearing in the immediate vicinity of the blood vessels, becoming more loosely arranged and showing variable amounts of necrosis in those portions farthest removed from the vascular channels.

The tumor cells themselves were small, fairly uniform in size, oval to round, with scanty cytoplasm. The scanty cytoplasm was one of the outstanding differential features of the small cell tumor. While a small to moderate number of the nuclei were dark staining and hyperchromatic, the greater number had vesicular appearing nuclei with finely divided chromatin material scattered through the nucleoplasm. Nucleoli were extremely rare. Mitotic figures in general were considered to be minimal in number, with only three of the 20 cases showing numerous mitotic figures. The cells were predominantly oval, but in about one-third of the cases there was equal admixture of round and oval forms.

In 17 cases the small cell tumor was of a pure type, in only three was there variability. In one, adenocarcinomatous differentiation was observed with an admixture of cuboidal and columnar cells having relatively abundant cytoplasm and a tendency to acinus formation; in a second, minimal evidence of squamous cell differentiation was a feature, and in a third there was no evidence of differentiation toward either of the types, but there was an admixture of relatively plump cells, some tending to be polyhedral with more cytoplasm than the characteristic cell of this tumor.

Stroma accompanying the tumor was usually scant. Vascularity as a rule was minimal, but was moderate in several and marked in one. Necrosis of tumor tissue was rather rare in one-half of the cases; it was moderate in one-third and marked in the remainder.

Tumor giant cells were relatively infrequent, and much less often seen than in squamous cell carcinoma. Tumor cells were identified within lymphatics in sections from the primary lung foci in 80 per cent of the cases, and in blood channels in 20 per cent. This relatively higher incidence of tumor cells in vascular channels is in correlation with the greater incidence of extrathoracic metastases in small cell carcinoma.

Adenocarcinoma: Gross Features: This group included eight cases, and constituted 16 per cent of the series analyzed. Only one adenocarcinoma originated in the main stem bronchus, three in epiarterial or hyparterial branch bronchi, and two were described as diffuse, with no bronchial focality demonstrated. The remaining two cases were insufficiently described to permit accurate localization of the primary tumor. Tumors of this type arose most frequently on the left side and in the left upper lobe. Two

were associated with occlusion of the bronchus. Bronchiectasis was described in two, and extension of tumor from lung to chest wall was noted in two cases. The highest incidence of pleural effusion was found in this category, being present in all but one case; the majority of these effusions were hemorrhagic. Invasion of the heart or pericardium was found in one-fourth of the cases, that is, in the same relative frequency as in the squamous cell and adenocarcinoma groups.

Histologic Features: The histologic findings were based on formalin-fixed, hematoxylin and eosin stained sections, and mucin stains were done in only two cases. Certain features were distinctive and limited to this type. These included: papillary architecture, acinus formation, production of mucin, signet-ring cells, and presence of cilia. These distinctive features were not present in all the tumors, and when present, showed considerable variability in amount and proportion. Half of the tumors showed considerable differentiation, as evidenced by papillary architecture, columnar cells, cilia, and formation of acini. The tumors which showed papillary architecture also showed ciliated and non-ciliated columnar cells, formation of numerous acini, and maximal secretory activity. Signet-ring cells, however, were more commonly seen in the less differentiated tumors. In general, the type and character of the metastases were similar to those of the primary lung tumor. In several of the less differentiated tumors, those with relatively few acini and little secretory activity, the cells were frequently seen in closely packed, squamous-like mosaics, but in none of the cases was there any clear-cut transition to either of the other two major tumor types.

In general, the tumor cells were moderate-sized and showed some variation in cell shape. All the tumors were composed in part of cuboidal cells; columnar cells in relatively large numbers were seen in one-half the cases, and polyhedral variations were seen in the majority of these tumors. The cytoplasm was relatively abundant, and almost all cases showed some degree of fine vacuolation of cytoplasm. Coarse vacuolation was seen in about half the cases. The nuclei of the tumor cells were oval to round, of moderate size in proportion to cell size, and the majority contained finely divided chromatin material and were vesicular, with a minority of the nuclei being darker and more solidly staining.

The presence of distinct nucleoli was a relatively prominent feature among the adenocarcinomas, with large and often multiple nucleoli being frequently seen. Mitotic figures were seldom noted. Only one of the eight cases displayed a moderate number of mitoses. Secretory activity was marked in three of the cases, being associated in each instance with papillary architecture and

numerous acini. As a group, and in comparison with the squamous cell variety, tumor giant cells were relatively infrequent and an inconspicuous histologic feature.

Necrosis of tumor tissue was relatively slight in comparison to this feature in the squamous cell and small cell groups. Tumor cells were seen either in blood or lymphatic channels at the sites of the primary tumor in approximately three-fourths of the cases.

Metastases

Extrathoracic spread could be demonstrated at time of autopsy in three-fourths of the 50 cases. The highest incidence of extrathoracic spread was in the small cell group (95 per cent), followed by the adenocarcinoma (62 per cent), and the squamous cell (59 per cent).

Regional hilar and tracheobronchial lymph node metastases were found in 88 per cent of the 50 cases, with the order of frequency being the same as that seen for the extrathoracic dissem-

TABLE 12
Extrathoracic Metastases in 50 Cases of Bronchogenic Carcinoma

Type	Total Cases	Cases with Extrathoracic Metastases	Per cent
Squamous Cell	22	13	59
Small Cell	20	19	95
Adenocarcinoma	8	5	62
TOTAL	50	37	74

Source: Autopsies, Letterman General Hospital, 1920-1948.

TABLE 13
Lymph Node Metastases in Bronchogenic Carcinoma
(50 Fatal Cases)

Present Series	From Letterman General Hospital			344 Collected Cases*	
Lymph Nodes	Squamous Cell	Small Cell	Adenocarcinoma	Cases	Per cent
Tracheobronchial	81	95	87	307	61.9
Abdominal (periaortic)	18	35	25	0	0
Cervical	9	30	25	47	14.0
Peripancreatic	13	5	0	8	2.4
Axillary	0	5	16	14	4.1
Peribiliary	4	5	0	0	0
Retroperitoneal	0	0	0	60	17.9
Inguinal	0	0	0	5	1.5
Pelvic	0	0	0	15	4.5

*Maher, Tenzel, Mitton and Mulligan.

ination: small cell, 95 per cent, adenocarcinoma, 87 per cent, and squamous cell, 81 per cent. Other lymph nodes which were the seat of metastatic tumor, in order of frequency, were: periaortic (abdominal), cervical, peripancreatic, axillary, and peribiliary (the last two of equal frequency) (Table 13). In general, the small cell carcinoma accounted for a greater percentage of lymph node metastases than either the adenocarcinoma or the squamous cell carcinoma.

Intracranial metastases were found in 21 of the 38 cases in which the brain was removed (Table 14). By category, the adenocarcinoma showed the highest incidence of brain metastases (50 per cent) with the squamous cell and small cell carcinomas (17 per cent and 13 per cent, respectively).

Other extrapulmonary metastases were found in 16 different anatomic locations. Of these, the adrenal was the most frequent site of metastasis, followed in order by the liver, pleura, bone, kidney, gastrointestinal tract, opposite lung, heart and pericardium, diaphragm, pancreas, peritoneum, thyroid, spleen, skin, gallbladder, and dura mater. The 13 metastases to the gastrointestinal tract included seven instances of direct extension to the esophagus from mediastinal tumor. Such extension was seen in the squamous cell and small cell groups, but not in the adenocarcinoma.

The squamous cell tumors had the highest incidence of metastases to heart and pericardium and to the kidney. Small cell carcinoma had the highest incidence of metastases to the lymph nodes, adrenal glands, liver, gastrointestinal tract, pancreas, thyroid, and spleen. The adenocarcinomas metastasized relatively more frequently to bone, pleura, opposite lung, diaphragm, and peritoneum. The only tumor in this series which was found to metastasize to the skin was an adenocarcinoma. The viscera demonstrating the lowest incidence of metastases were spleen and gallbladder.

The data show that bronchogenic carcinomas of the three major

TABLE 14

Brain Metastases in 50 Cases of Bronchogenic Carcinoma.

Type	Total Cases	Number of Brains Examined	No. with Metastases	Per cent with Metastases
Squamous Cell	22	17	3	17
Small Cell	20	15	2	13
Adenocarcinoma	8	6	3	50
TOTAL	50	38	8	21

Source: Autopsies, Letterman General Hospital, 1920-1948.

types spread by direct extension and by lymphatic and blood channels. It is also apparent that the squamous cell type shows the greatest tendency to remain intrathoracic, that lymph node metastasis is seen more frequently with the small cell carcinoma, and that metastasis to such sites as the adrenal gland, bone, and pancreas (hematogenous metastases) is more usual from small cell carcinoma and adenocarcinoma than from squamous cell carcinoma. A higher incidence of hematogenous spread by the squamous cell tumor over the other two types was seen in only one organ, the kidney.

Colonel Kenneth F. Ernst, Chief of the Laboratory, and Major Helmuth Sprinz, Chief of the Pathology Section, both of Letterman General Hospital, San Francisco, advised concerning this study.

TABLE 15

Extrapulmonary Metastases in Bronchogenic Carcinoma

(50 Fatal Cases)

Present Series	From Letterman General Hospital				334 Collected Cases*	
Organ	Squamous Cell Per cent	Small Cell Per cent	Adeno-carcinoma Per cent	Per cent of All Cases	Cases	Per cent
Adrenal	36	60	50	48	106	31.7
Liver	31	55	16	38	120	35.9
Pleura	31	25	50	32	78	23.3
Bone	22	35	37	30	103	30.8
Kidney	31	25	16	26	66	19.7
Gastrointestinal Tract	18	40	16	26	36	10.7
Opposite Lung	18	25	37	24	65	19.4
Heart and Pericardium	27	20	25	24	47	14.0
Diaphragm	13	15	37	18	18	5.4
Pancreas	4.5	24	16	16	22	6.5
Peritoneum	0	10	25	8	16	4.8
Thyroid	9	10	0	8	16	4.8
Spleen	4.5	10	0	6		9.0
Skin	0	0	16	2	22	6.5
Gallbladder	0	5	0	2	4	1.2
Dura Mater	4.5	0	0	2	0	0

*Maher, Horn, Tenzel, Mitton and Mulligan.

SUMMARY AND CONCLUSIONS

There was an increase in the percentage of bronchogenic carcinoma as proved at autopsy at Letterman General Hospital from 1.2 in the decade 1920-1929 to 2.7 in the period 1940 through 1948.

The average duration of the disease was 11.7 months. The average duration for the squamous cell type was 13.6 months, the small cell type, 5.6 months, and the adenocarcinoma type, 21.5 months.

The onset of cough later in life or change in an already established cough was the most frequent first symptom. Fever and leukocytosis were common in cases of all cell types.

Positive evidence of a pulmonary lesion was present in all cases in which roentgenograms were taken. In 68 per cent this was in the form of parenchymal opacity, and in 20 per cent, of pleural effusion.

Bronchoscopic examination was done late in the course of the disease in many cases and exploratory thoracotomy in only four. It is suggested that earlier diagnoses would result if lesions which had not changed for the better in three weeks' time were investigated by bronchoscopy and by cytologic examination of sputa by the Papanicolaou method. If bronchoscopic examination is not decisive, it is believed that early thoracotomy is indicated.

The average delay in diagnosis was found to be approximately 7.5 months from the onset of symptoms. The patient's delay accounted for 6 months and the physician's delay for 1.5 months.

The squamous cell type of bronchogenic carcinoma predominated in this series with 44 per cent; the small cell type was second with 40 per cent, the adenocarcinoma type was third with 16 per cent. In six of the cases, a mixture of the three primary types was found.

Seventy-eight per cent of the tumors arose centrally.

Gross and microscopic features of each of the three tumor types are presented.

RESUMEN Y CONCLUSIONES

Ha habido un aumento en el porcentaje de carcinoma broncogénico según lo prueban las autopsias en el Hospital General Letterman, desde 1.2 que hubo en la década de 1920-1927 a 2.7 en el periodo de 1940 a 1948.

El término medio de duración de la enfermedad ha sido de 11.7 meses. Para el de celdillas escamosas ha sido de 13.6 meses; el de pequeñas celdillas de 5.6 meses y el adenocarcinoma ha tenido una duración de 21.5 meses.

El síntoma más frecuente ha sido la aparición de tos en la madurez de la vida o más allá de ella o cambios en la tos ya establecida.

La fiebre y la leucocitosis fueron comunes en todos los tipos celulares.

En todos los casos en que se tomaron radiografías hubo evidencia positiva de lesión pulmonar. En 68 por ciento de los casos esto fué en la forma de opacificación parenquimatosa y en 20 por ciento de derrame pleural.

El examen broncoscópico fué hecho tarde en el curso de la enfermedad en muchos casos y solo se hizo toracotomía exploradora en cuatro.

Se sugiere que un diagnóstico más temprano resultaría si las lesiones que no cambian en un término de tres semanas, mejorando, fuesen investigadas por broncoscopía y por examen citológico de los esputos, por el método de Papanicolaou. Si la broncoscopía no es decisiva está indicada la toracotomía exploradora.

La dilación media en el diagnóstico fué de 7.5 meses desde el principio de los síntomas. De esta dilación se debieron al enfermo aproximadamente seis meses y al médico 1.5 meses.

El carcinoma de celdillas escamosas predominó en esta serie con el 44 por ciento; el de celdillas pequeñas siguió con 40 por ciento. El tipo de adenocarcinoma fué el tercero con 16 por ciento.

En seis de los casos una mezcla de los primarios se encontró.

Setenta y ocho por ciento de los tumores se desarrollaron centralmente. Se presentan aspectos macro y microscópicos de los tres tipos de tumores.

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The Humanics of Medicine*

THE HONORABLE WENDELL B. FARRIS
Chief Justice Supreme Court, British Columbia

It is a particular pleasure and honour to be asked to address this distinguished gathering tonight. This pleasure is accentuated by the fact that so many of you come from that great country, our good neighbour to the south. For over 100 years, with an unguarded borderline of 3,000 miles, we have lived in peace and mutual understanding. What a great world lesson it is in this age which might be referred to as the "Atomic Age," amid dissension and strife between nations, that a great power and a smaller power can live in goodwill side by side.

We have in common one single great objective—Peace on Earth, and goodwill towards all. Neither your country nor my country desire aggrandizement. We have no thought of aggression.

Over a period of one hundred years we have had peace, and over this period of time our friendship and understanding have continued to grow so that today our mutual trust and regard for each other is greater than at any time in history. Our thoughts are blended together as one, to strive for the benefit of humanity.

> "Three thousand miles of border, one hundred years of peace,
> In all the page of history, what parallel to this?
> Godspeed that surely dawning day, that coming will define,
> When all the nations of the earth shall know such borderline!"

On being asked to address you, it was suggested that I might choose a topic having something to do with how the layman views present day medical treatment.

I presume many of you are bridge players and know that there has been an attempt to make the playing of bridge a science, with many books written on the rules and the science of bridge. Recently, one of the great bridge experts, Mr. Blackwood, has written a number of articles to show how these rules of bridge can never reach an exact science because of the different mentality of those using them. In other words, the human side plays a most important part in even the game of bridge. Today, the study of medicine is becoming more and more scientific. But in the treatment, the human side, as in bridge, does, and will continue to play an important part in the doctor's life. Mr. Blackwood is now writing a book known as "The Humanics of Bridge"

*Presented before a joint meeting of the Pacific Northwest Chapter of the American College of Chest Physicians and the American Trudeau Society, Vancouver, British Columbia, Canada, October 27, 1949.

and I thought that a suitable title for my address tonight would be "The Humanics of Medicine."

We have, during recent years, heard a great deal concerning state medicine. Whether you realize it or not, state medicine is here today, and it is here to stay. State medicine has been gradually extending for over 100 years and the question today is not whether there will be state medicine, but how far will it extend, and that will depend upon the individual practising members of the profession.

State medicine began its development with the early public health measures and as far as I can trace it in this country, the beginning was in 1667 when a meeting was called in the City of Quebec to consider the quality and weight of bread. In 1707 regulations were passed for the inspection of meat. No butcher was permitted to kill an animal without first informing. In 1721 our quarantine service began, when the colonial government at Quebec adopted a regulation requiring the ships coming from plague-striken Marseilles or other Mediterranean ports to anchor in the stream and fire a gun at intervals of 15 minutes to announce their arrival. Physicians then boarded the ship and inspected the passengers and crew to see whether evidence of disease could be found.

Under this law of 1721, it was forbidden for any person to come ashore from the ship, and corporal punishment was provided as a penalty for violation of this regulation. On one occasion a war vessel called "The Leopard" was found to be so infected with disease that the military authorities set fire to it and let it founder in the harbour.

Our early history is full of interesting episodes which show that the care of the health of the people of Canada has ever been of primary concern to the Government.

In 1867 when Canada became a Confederation, public health service was an established institution of government and under the British North America Act which is our Constitution, the Provinces and the Federal Government had their functions in respect to public health defined.

In 1919, the Act establishing the Department of Health came into effect and there were transferred to it various functions at that time distributed among no fewer than 15 different Federal departments. The services created, or transferred to the Department of Health when it was created in 1919, were: Quarantine Service (including Leper stations and Immigration medical service); Administration of the Food and Drugs Act; Administration of the Opium and Narcotic Drugs Act; Administration of the Proprietary and Patent Medicine Act; Marine hospital services; Venereal disease control; Child welfare; Statistics; Housing; Med-

ical examination of civil servants. Subsequently there have been added: The laboratory of Hygiene and Public Health Engineering; The child and maternal Hygiene Division; The Division for the study of the control of epidemics; The Division of Industrial Hygiene; The Division of Publicity and Health Education. How effective the medical examination of civil servants has been is indicated in the Civil Service of Canada alone. By carefully checking, the Department of Health has succeeded in reducing the lost days in a year by 122,000, or the equivalent of 400 officials for a whole year.

During the War our entire Military Forces were under state medicine and today in the City of Vancouver, one of the most modern and scientific hospitals in the whole of Canada is a State Hospital—Shaughnessy Military Hospital.

Your Government on the American side, and our Government here, are day by day increasing their scope in health protection. The laboratories of the Governments are being used to the full extent in assisting medical research along scientific lines.

Today it is recognized that the laboratory is as necessary to a modern doctor's office as a stethoscope was in earlier days, and the doctor of today is becoming more and more a scientist. While there are many opportunities for the young doctor of today, in country districts, these young physicians do not desire to practice there because of the lack of the assistance of a laboratory. In Kansas, under the active efforts of Dr. Murphy, head of the Medical College of that state, a new system is being developed and that is—in the country districts the residents are being asked to cooperatively raise the funds to establish in their particular community, a doctor's residence, having attached to it a small but efficient laboratory and x-ray equipment, the result being that the young doctor is only too glad to take advantage of the opportunity afforded, and the country doctor is no longer a problem in that state.

I have emphasized throughout the part that science is today playing in medicine. In addressing a group of graduating nurses a short time ago, I pointed out to them the advantages of a nurse in modern times, when hospitals of today are really becoming laboratories, but I warned the nurses that no scientific institution could ever replace the cheerful disposition of a nurse and the necessity of a nurse retaining all of the human qualities of a Florence Nightingale, and that she must never forget that scientific development does not change the nature of a human being. The will to live today is as essential in a patient as it ever was, and the cheerfulness, the encouragement and sympathetic treatment given by a nurse may be the determining factor in whether a patient shall live or die.

Today, a young doctor must be a scientist. He must serve his

term in a Medical College. He must serve his internship, then practise in his chosen branch of medicine with an older practitioner, and then take his two years postgraduate course before he is entitled to certification in the particular branch of medicine that he has chosen. In this long course in which science plays such a predominant part, it is little wonder if the young doctor who finally branches out for himself is, perhaps, a little contemptuous of human weaknesses and feels himself somewhat superior to his patient, and is inclined to treat his patient on an allotted time basis and as though the patient were but an experimental guinea pig upon which he can practise his long and hard-earned scientific knowledge.

You may not like what I am going to say, but from my observation, this has been the trend of the practise of medicine, and with that tendency has developed the inclination toward state medicine. Leave out the human equation and rely only on the scientific knowledge of medicine and complete state medicine will follow as surely as night the day.

You have asked me for the layman's view and that brings me to the subject of my address—"The Humanics of Medicine." It is my view that in each Medical College there should be a new chair established, and that is a teaching of the humanics of medicine. My first suggestion would be to the young doctor (and this he cannot have impressed upon him too strongly), during his whole career in practice, he should never have more than one patient. Every patient that goes to a doctor, in so far as he or she is concerned, is the most important patient in the world, and when the doctor is dealing with such patient, regardless of how short a time he is going to spend with the patient, he should make that individual feel that time is not an object with him—other patients mean nothing to him—all the doctor is concerned with is the condition and health of the person he is then dealing with. In my own private practice as a lawyer, clients used to frequently say, "I know you are a busy man—my business may not seem important to you, and I do not want to take up your time." I invariably replied, "Nothing is more important to me at the present time than your business. You have all the time there is." I found that it did not take me a moment longer to deal with him in this manner than by indicating an impatience, the result being that the client went away feeling that if any business was going to be neglected by me, it was not his. I care not who may be important or unimportant as far as the community generally, is concerned. We each are important to ourselves, also remember a sick person is never normal.

A doctor must make a patient feel at home and that he is not viewing the case from a cold scientific standpoint, but rather is

taking a personal interest in him. How can this be accomplished? First, if I were a doctor, when my nurse made a record of the case, I would include such questions as: the size of the family, the children, their names, their ages, what the children are doing, their health, etc. Then when this patient comes to the doctor this record should be placed before him. A glance at this and the doctor should obtain such information as will enable him to open the interview on a pleasant, personal vein. A patient is always nervous. If, instead of being brusquely greeted by the doctor, the patient was asked, say, "Well, what do you hear from Mary at Havergill?"—the patient's attention is immediately distracted, he loses his tenseness, and a moment later when his own case is discussed, he is at ease. And when he leaves, he has the feeling that a doctor who is so human and so thoughtful of small detail, is one worth having.

Do not be afraid to suggest consultations. If you see that a patient does not seem to be altogether satisfied, suggest to him that he might like to have a consultation. You may be the head of a clinic and have the men you think are outstanding in that particular branch of medicine, and while you may suggest to the patient a member of your clinic, at the same time do not hesitate to say that perhaps he would like someone else. This creates a confidence in a patient which you cannot understand unless you yourself have been a patient. The individual believes because you have done this, your first and paramount thoughts are his best interests, and he is safe in the hands of a man who is big enough to make such a proposal.

Here is another suggestion. It is frequently noted that a doctor who is engaged in hospital work in the morning will have his appointment book for the afternoon filled with office consultations and in some busy doctor's offices you will see 15 or 20 waiting at the opening of the afternoon consultations, say at 2 o'clock. This gives the appearance of the medical examinations being carried on, not for the benefit of the patient, but as a race to see how many can be examined within a given space of time. How much better it would be if these appointments were staggered throughout the afternoon and that no more than two or three should ever be waiting at the same time. Sometimes a patient will arrive without an appointment. He is from out-of-town, or he is very busy, but, nevertheless, extremely worried. Five or 10 minutes given to him would send him away happy. A doctor would not lose prestige or gain the resentment of the waiting patients if he were to step out into the waiting room and in a smiling way, briefly explain the circumstances and ask the other patients if they would mind waiting a few minutes while he saw this patient. People are naturally cooperative when properly approached. They

realize that a doctor cannot travel on schedule like a train. They like to see their doctor be thoughtful and are only too glad to assist when approached in the proper manner.

Recently, one of the world's greatest heart specialists visited Vancouver and those who came in contact with him must have been greatly impressed with his exemplification of what I said about a doctor only having one patient, because, regardless of his great eminence, any person being examined by him could, during that examination, only believe the patient's best interest was alone being considered.

I do not mean to imply that a doctor should appear to be a simpering idiot. He must be firm. He must be dignified, but smiling courtesy, a thoughtful, human interest, adds to, rather than takes away the firmness and dignity a doctor should have.

You must never forget even in this great age of scientific medical advancement that one must remain humble in the knowledge there is still so much to learn.

The doctors mentioned by Jonathan Swift so many years ago as being the three great ones of that time, are still the three great doctors at present, his words being, "The best doctors in the world are Doctor Diet, Doctor Quiet and Doctor Merryman."

Remember, gentlemen of the medical profession, that in your progress along modern scientific lines, you can even now only become great doctors when you live up to the tribute paid to the medical profession, long ago, by one who owed so much to physicians, that wistful Scots writer, Robert Louis Stevenson who said:

"There are men and classes of men that stand above the common herd; the soldier, the sailor, and the shepherd not infrequently: the artist rarely; the physician almost as a rule. He is the flower (such as it is) of our civilization; and when that stage of men is done with, and only remembered to be marveled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited in the virtues of the race.

"Generosity he has, such as is possible to those who practice an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarrassments; and what are more important, Herculean cheerfulness and courage. So it is that he brings air and cheer into the sickroom, and often enough, though not so often as he wishes, brings healing."

And so I say to you in conclusion, continue your great work, unite the science and the humanics of medicine to the greater glory of your noble profession:

"Build on, and make thy castles high and fair, rising and reaching upwards to the skies."

College Chapter News

FLORIDA CHAPTER

The annual meeting of the Florida Chapter was held on April 23 at the Hollywood Beach Hotel, Hollywood, Florida. The officers elected for the coming year are:

Arnold S. Anderson, M.D., St. Petersburg, President
Howard K. Edwards, M.D., Miami, Vice-President
Alexander Libow, M.D., Miami Beach, Secretary-Treasurer.

Dr. Nathaniel M. Levin, Miami, has been appointed chairman of the program committee for the next meeting of the chapter.

GREEK CHAPTER

The Greek Chapter of the College held a meeting in Athens on April 1st at which time the following officers were elected:

Nicholas Yannopoulos, M.D., President
Eugene Joannides, M.D., Vice-President
John Lameras, M.D., Secretary-Treasurer.

ILLINOIS CHAPTER

At the annual meeting of the Illinois Chapter held in Springfield on May 23, the following officers were elected for the ensuing year:

Edwin R. Levine, M.D., Chicago, President
Charles K. Petter, M.D., Waukegan, Vice-President
W. J. Bryan, M.D., Rockford, Secretary-Treasurer.

MICHIGAN CHAPTER

The Michigan Chapter of the College held its annual meeting on May 18 at which time the following officers were elected:

Cletus J. Golinvaux, M.D., Monroe, President
Benjamin E. Goodrich, M.D., Detroit, Vice-President
Constantine P. Mehas, M.D., Pontiac, Secretary-Treasurer.

OHIO CHAPTER

The annual meeting of the Ohio Chapter of the College was held at the Hotel Statler in Cleveland on May 17. The following officers were elected for the year 1950-1951:

E. F. Conlogue, M.D., Dayton, President
Joseph Stocklen, M.D., Cleveland, Vice-President
Harold G. Curtis, M.D., Cleveland, Secretary-Treasurer.

PORTUGUESE CHAPTER

The annual meeting of the Portuguese Chapter of the College was held Saturday, March 18, at the University of Coimbra, under the direction of the Regent, Professor Lopo de Carvalho. The following program was presented:

Professor Agusto Vaz Serra, President, presiding

"New Technique for the Angiopneumographic Examination,"
Prof. Lopo de Carvalho and Dr. Carlos Vidal.
"Seriographs for the Study of Circulation,"
Dr. Aires de Sousa.
"A Case of Foreign Body,"
Dr. Costa Quinta.
"A Clinical Case,"
Dr. Antonio Araujo.
"The Jugular Vein Must be Preferred for the Contrast Substance in the Angiopneumographic Examination,"
Prof. Lopo de Carvalho, Filho.
"Two Cases of Bronchial Adenoma,"
Dr. Ferreira dos Santos.
"Schematic Representations of the Force Exerted on the Cavity Walls,"
Dr. Lopo Cancella and Dr. Lopo de Carvalho, Filho.
"Upper Lobectomy: Consideration of Two Cases,"
Dr. Bello de Morais.
"Angina-pectoris in Young Syphilitic Patients,"
Dr. Luis Providencia.
"Pericarditis with Effusion and Streptomycin,"
Prof. Agusto Vaz Serra.
"Consideration of Pneumoperitoneum in the Treatment of the Vertex and Base Cavities,"
Prof. Agusto Vaz Serra.
"Consideration of a Clinical Case,"
Dr. Jorge Santos.

A luncheon and business meeting was held after the scientific session. The following officers were elected for the ensuing year:

Antonio S. Araújo, M.D., Porto, President
Ladislau Patricio, M.D., Guarda, Vice-President
Lopo Cancella, M.D., Lisbon, Secretary-Treasurer.

POTOMAC CHAPTER

At the annual meeting of the Potomac Chapter held in Baltimore on April 26, the following officers were elected for the ensuing year:

Hugh Whitehead, M.D., Baltimore, Maryland, President
Daniel Finucane, M.D., Glenn Dale, Maryland, Vice-President
Milton B. Kress, M.D., Baltimore, Maryland, Secretary-Treasurer.

PUERTO RICO CHAPTER

The Puerto Rico Chapter held its annual meeting in Santurce on December 17, 1949. The following officers were elected for the coming year:

E. Martinez Rivera, M.D., Hato Rey, President
Jose Soto Ramos, M.D., Rio Piedra, Vice-President
Fernando Padró, M.D., Santurce, Secretary-Treasurer.

NEW YORK STATE CHAPTER

At the annual meeting of the New York State Chapter of the College held in New York City on May 11, the following officers were elected:

David Ulmar, M.D., New York City, President
Clyde George, M.D., Buffalo, First Vice-President
Charles E. Hamilton, M.D., Brooklyn, Second Vice-President
Harry Golembe, M.D., Liberty, Secretary-Treasurer.

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter was held at the University of Virginia, Charlottesville, on March 30. The officers elected for the coming year are:

George Welchons, M.D., Richmond, President
J. B. Nichols, M.D., Catawba, Vice-President
M. F. Brock, M.D., Norfolk, Secretary-Treasurer.

College Chapter News

Dr. George M. Curtis, chairman of the Department of Research Survey at the Ohio State University College of Medicine was selected as one of two persons to receive the 1950 recognition award presented by the Professional Inter-Fraternity Council at Ohio State University. Dr. Curtis also was chosen for the 1950 honor award of the Mississippi Valley Medical Society.

Dr. Leo G. Rigler, Minneapolis, Minnesota, presented a paper on "Cancer of the Lung" at the annual meeting of the North Dakota State Medical Association held in Grand Forks, May 27-30, 1950.

Dr. L. Brull, Liege, Belgium, is president of the International Conference on Gerontology which was held in Liege, June 9-12, 1950.

Dr. John B. Andosca, formerly of the Boston Sanatorium, Mattapan, Massachusetts, has been appointed medical director and assistant superintendent of the Cambridge Sanatorium, Cambridge, Massachusetts.

The Hyman Spector lectures were initiated by St. Louis University on April 12. Dr. Jay Arthur Myers, Minneapolis, Minnesota spoke on "Immunity and Tuberculosis—Thirty Years of Observation."

Dr. Fred Wittich, Minneapolis, Minnesota, presented a paper entitled "Treatment of Acute Allergy in General Practice" at the annual meeting of the South Dakota State Medical Association held in Huron, May 21-23.

Dr. Willard Van Hazel and Dr. Francis L. Lederer of Chicago were honored at the twenty-fifth anniversary observance of the opening of the University of Illinois Research and Educational Hospitals on April 1. They have served continuously since April 1, 1925 and were presented keys by Dr. Andrew C. Ivy, vice-president of the university in charge of the Chicago Professional Colleges.

CORRECTION

Co-author with Dr. Alfred Goldman of the paper on "Benign Tumors of the Lungs with Special Reference to Adenomatous Bronchial Tumors," which appeared in the June, 1950 issue, should read "Charles L. Connor, M.D.," instead of "Charles L. Conner, M.D."

LOUIS MARK, M.D., F.C.C.P.

PRESIDENT

American College of Chest Physicians

1950-1951

DR. LOUIS MARK INSTALLED AS COLLEGE PRESIDENT

Dr. Louis Mark, Columbus, Ohio, a Charter Member of the American College of Chest Physicians, became the Thirteenth President of the College at the Sixteenth Annual Meeting held in San Francisco, June 22-25.

Dr. Mark attended the first meeting of the organization held in Albuquerque, New Mexico on August 10, 1935 and has been an active member, holding many offices in the College and serving on many important committees. He was the first President of the Ohio Chapter of the College and served as Governor of the College for the State of Ohio and Regent for the district before being nominated for the office of Second Vice-President.

Dr. Mark was born in Duluth, Minnesota on December 11, 1890. He attended grade school and high school in Ironwood, Michigan and graduated from Marquette University Medical School in Milwaukee, Wisconsin in 1915. Dr. Mark interned at Milwaukee Children's Hospital and at the Cincinnati General Hospital. He did postgraduate work and research in physiology of the lungs with Dr. William Snow Miller and Dr. Kennon Dunham at the University of Wisconsin in 1916. He later became associated with Dr. Dunham in private practice in Cincinnati, specializing in diseases of the chest since 1918. Dr. Mark served as Contract Surgeon for the United States Army in 1918. Since 1919, he has been Medical Director of Rocky Glen Sanatorium for Tuberculosis in McConnelsville, Ohio. He was chest expert to the Veterans Administration during the years 1919-1924. In 1923 Dr. Mark was made the first President of the Ohio Tuberculosis Hospital Superintendents Association. He has served as chief of the chest department of the White Cross Hospital, Columbus, Ohio since 1928 and served as medical director of the Jane M. Case Tuberculosis Sanatorium, Delaware, Ohio from 1934 to 1944. He is a member of the Columbus Academy of Medicine, Ohio State Medical Association, American Medical Association, American College of Physicians and is the author of many papers on diseases of the chest.

Dr. Mark is also a member of the Rotary Club, American Contract Bridge League (President, 1949), Variety Club, Athletic Club of Columbus, Winding Hollow Country Club, Excelsior Club, Cavendish Club of New York, and of the Masonic Order.

Medical Service Bureau

POSITIONS AVAILABLE

Positions open for physicians in large tuberculosis hospital. Salaries from $4,800 to $7,320 annually. Must be eligible for license to practice in Georgia. Contact Personnel Office, Battey State Hospital, Rome, Georgia.

Residency in division of medicine in chest service university hospital. Duties include work in field of various chest diseases. Splendid opportunity. One year beginning July 1. $250 per month salary. Credit toward American Board of Internal Medicine. Please address Box 213A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Assistant Medical Director wanted for Nebraska Hospital for the Tuberculous; 220 bed hospital offering all phases of treatment of tuberculosis. Knowledge of tuberculosis preferred. Must be eligible for Nebraska license. Living quarters and maintenance furnished. Salary approximately $5,000 yearly. Inquire Medical Director, Nebraska Hospital for the Tuberculous, Kearney, Nebraska.

Opportunity for Chest Physician: Kentucky has a new progressive tuberculosis program. Included in the program is the opening of five new one-hundred bed tuberculosis hospitals by August 1, 1950. Medical Directors are needed at once. Salary $7,000 annually with full maintenance. Call, wire or write T. F. Moore, Jr., Executive Director, State Tuberculosis Sanatoria Commission, Frankfort, Kentucky.

Junior Resident on thoracic service (approved by AMA 3 years for pulmonary disease). If objective is specialty in thoracic diseases, a recent graduate with rotating internship and residency in medicine is required. If objective is thoracic surgery, recent graduate with rotating internship and residency in surgery is required. Santa Clara County Hospital is a 500 bed institution with a tuberculosis service of 130 beds and a large out-patient chest department. Salary is $235 per month plus three meals and laundry. For further information apply to Dr. Charles L. Janne, Chief of Thoracic Service, Santa Clara County Hospital, San Jose, Calif.

There will be several vacancies for resident physician on medicine at Seton Hospital effective January 1, 1951. Seton Hospital is a municipal tuberculosis institution with 450 beds for adults and children. The residency is approved by the Council on Medical Education of the American Medical Association. It is affiliated with the Morrisania City Hospital for training in non-tuberculous chest diseases where residents are on rotation service. The Hospital also has a teaching affiliation with the New York Medical College, Flower and Fifth Avenue Hospitals. The salary is $1,560 with single maintenance. Those interested please write or telephone the medical Superintendent, Seton Hospital, 3221 Henry Hudson Parkway, Bronx, N. Y.

Vacancy available for a full time physician in charge of tuberculosis at the Hospital de Medicina y Cirugia Toracica, Hato Tejas, Puerto Rico. Training in tuberculosis desirable. Starting salary $6,000 annually, opportunity for advancement, unfurnished house available. Knowledge of Spanish not necessary. Married or single. For further information please address Dr. E. D. Maldonado Sierra, Calle Mejico No. 17, Hato Rey, Puerto Rico.

Residency in thoracic surgery in Oregon available beginning July 1. For further information please address Box 214A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

POSITIONS WANTED

Associate or partnership in chest work. Experienced chest specialist. Willing to make investment. Now holding responsible position. American and a graduate of a Class A medical school. Excellent references. Please address Box 245B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

White Puerto Rico physician, graduated from the Medical College of Virginia, six years experience in general practice and ten years experience in internal medicine and diseases of the chest, desires position. Licensed to practice in New York and eligible to a license in Ohio either by reciprocity or by taking Board examinations. Please address Box 246B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

COLLEGE JOURNAL IN MICROFILM FORM

The American College of Chest Physicians has entered into an agreement with University Microfilms, Ann Arbor, Michigan, to make available to libraries issues of the College journal "Diseases of the Chest."

One of the most pressing problems facing all types of libraries today is that of providing adequate space for a constant flood of publications. Periodicals pose an especially difficult problem because of their bulk and number.

Microfilm makes it possible to produce and distribute copies of periodical literature on the basis of the entire volume in a single roll, in editions of 30 or more, at a cost approximately equal to the cost of binding the same material in a conventional library binding.

Under the plan, the library keeps the printed issues unbound and circulates them in that form for from two to three years, which corresponds to the period of greatest use. When the paper copies begin to wear out or are not called for frequently, they are disposed of and the microfilm is substituted.

Sales are restricted to those subscribing to the paper edition, and the film copy is only distributed at the end of the volume year.

The microfilm is in the form of positive microfilm, and is furnished on metal reels, suitably labeled. Inquiries concerning purchase should be diretced to University Microfilms, 313 North First Street, Ann Arbor, Michigan.

POSTGRADUATE COURSE IN BRONCHOESOPHAGOLOGY

The University of Illinois College of Medicine announces a fall postgraduate course in Bronchoesophagology which will be supervised by Doctors Paul Holinger and Albert Andrews.

This course will be held from September 18 through September 30, 1950. For application forms and further information communicate with the Department of Otolaryngology, University of Illinois, 1853 West Polk Street, Chicago 12, Illinois.

SANATORIUM DIRECTORY

The sanatoria listed in this section are among the finest private sanatoria in the United States. They are prepared to offer private, individual, specialized care to your patients.

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Jay Arthur Myers, M.D., F.C.C.P., Chairman, Editorial Board.

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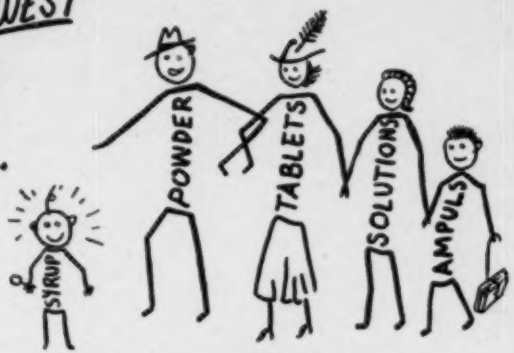

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